ARCHIVES of INTERNAL MEDICINE

VOLUME 71 JANUARY 1943 NUMBER 1

COPYRIGHT, 1943, BY THE AMERICAN MEDICAL ASSOCIATION

SUPERNORMAL CIRCULATION IN RESTING SUBJECTS (HYPERKINEMIA)

WITH A STUDY OF THE RELATION OF KINEMIC ABNORMALITIES TO THE BASAL METABOLIC RATE

ISAAC STARR, M.D.
AND
LEON JONAS, M.D.*
PHILADELPHIA

During the past fifteen years, estimations of basal, or resting, cardiac output, first by the ethyl iodide method and later by the ballistocardiogram, have been made for about 1,400 subjects. In this work we had both immediate and remote objectives in view. The first of the latter was attained when we secured 100 subjects with subnormal circulation and discussed the clinical significance of the abnormality.[1] It has taken us three years longer to assemble data on 100 subjects with circulation above the normal, and a chief feature of this report is an account of this group.

In addition, using all our data, we have studied the relation between abnormalities of the amount of the resting circulation and of the basal metabolic rate.

By our studies important abnormalities have been demonstrated in many patients who have had symptoms referable to their circulation without detected organic disease. As these abnormalities seem fundamental to an understanding of the group, cases in which they occurred will be given special emphasis.

METHODS

The technics used have been reported in detail,[2] and their description need not be repeated We do not regard methods for determining car-

* Woodward Fellow in Physiological Chemistry.

The completion of this work was aided by a grant from the Daland Fund of the American Philosophical Society.

From the Research Department of Therapeutics, the William Pepper Laboratory of Clinical Medicine, and the Medical Division of the Hospital of the University of Pennsylvania.

1. Starr, I., and Jonas, L.: Syndrome of Subnormal Circulation in Ambulatory Patients, Arch. Int. Med. **66**:1095-1111 (Nov.) 1940.

(Footnotes continued on next page)

diac output as highly accurate, but they are certainly accurate enough for the present purpose, to divide clinical patients into three groups, with circulation normal, above normal and below normal.

All tests were made with the subject supine and after a rest period of fifteen minutes or longer. At first all estimations of cardiac output were performed before breakfast; in recent years they have been performed during the morning or afternoon, two hours or more after a light meal.

Our normal standards have been published.[3] In their calculation Suter's autopsy data on aortic size were employed as a factor in the estimations of cardiac output by the ballistocardiogram. The use of this factor has been criticized and strong evidence obtained that the aorta in living persons is larger than our estimate of it.[4] To correct for this error would raise the calculated cardiac output about 20 per cent. But in the past our estimations of the circulation of patients have usually been recorded as percentage derivations from the expected normal, and we plan to continue this method. The results would not be changed by employing the correction suggested by Cournand and associates, as both normal and abnormal values would be raised proportionately.

The boundaries of the normal zone are 22 per cent from the mean. The result of each method has been judged by its own standard, and both will be expressed in deviation from the normal in percentage. Thus all patients included in this series had circulations which exceeded the expected normal for their weight by 23 per cent or more.

Of our 100 patients, the estimation was made for 25 by the ethyl iodide method and for the remainder by the ballistocardiogram. Typical records of the latter are shown in figure 1. The great majority of the conclusions in this paper can be justified by results obtained by both methods.

When the ethyl iodide method was in use, prior to 1936, estimations of basal metabolic rate were made simultaneously with estimations of

2. (*a*) Starr, I., Jr.; Collins, L. H., and Wood, F. C.: Studies on the Basal Work and Output of the Heart in Clinical Conditions, J. Clin. Investigation **13**:13-43 (Jan.) 1933. (*b*) Starr, I.; Rawson, A. J.; Schroeder, H. A., and Joseph, N. R.: Studies on the Estimation of Cardiac Output in Man, and of Abnormalities of Cardiac Function, from the Heart's Recoil and the Blood's Impacts: The Ballistocardiogram, Am. J. Physiol. **127**:1-28 (Aug.) 1939. (*c*) Starr, I., and Rawson, A. J.: The Vertical Ballistocardiograph: Experiments on the Changes in the Circulation on Arising, with a Further Study of Ballistic Theory, ibid. **134**:403-425 (Sept.) 1941.

3. Starr, I., and Schroeder, H. A.: The Ballistocardiogram: II. Normal Standards, Abnormalities Commonly Found in Diseases of Heart and Circulation, and Their Significance, J. Clin. Investigation **19**:437-450 (May) 1940.

4. Cournand, A.; Ranges, H. A., and Riley, R. L.: Comparison of Results of the Normal Ballistocardiogram and a Direct Fick Method in Measuring the Cardiac Output in Man, J. Clin. Investigation **21**:287-294 (May) 1942.

cardiac output. In recent years the two tests have not been made simultaneously, but always within a few days of each other. Also, the basal metabolic rate has not been estimated in every case. Data on this rate are available for only 55 of the 100 patients with circulation exceeding the normal.

The absolute amount of cardiac output is meaningless without knowledge of the size of the subject. Estimations of basal metabolic rate are related to the body surface for a good physiologic reason, for heat is lost from the surface of the body. Many authors similarly refer the cardiac output to body surface, although this reason does not apply with the same force, for the elimination of heat is only one of many functions of the circulation. In our data [5] the normal subgroup is more homogeneous when the cardiac output is referred to body weight, and so we report our results in terms of weight.

One must consider using ideal [5] rather than actual weight. One can argue that variation in the weight of any patient depends in large part on difference in the amount of fatty tissue. Fat has so small a blood supply that alterations in its amount would affect the magnitude of the circulation very little, a viewpoint supported by our results in emaciated persons. This conception raises the question, Would not a better normal standard be achieved by expressing the amount of the circulation in terms of ideal weight rather than of actual weight? If ideal weight is used, our series of patients with hyperkinemia becomes much smaller, only 54 of the 100 having a circulation above normal in terms of their ideal weight.

We see only one way to decide such a question and that is in terms of utility. Our procedure has been influenced by experience with the estimation of basal metabolic rate. Fat also has a low metabolic requirement, but the accepted procedure is to estimate metabolic rate in terms of actual, not ideal, surface area, and the present standards have proved useful. If the ideal value is used, many subjects now judged abnormal are found to be within the normal range. This analogy, together with the uncertainties inherent in estimating ideal weight correctly, have inclined us to use actual weight until data concerning utility can determine which is better.

As in the previous investigation, many persons other than ourselves have contributed to the data used, and their names have appeared in previous publications.[6] The estimations of circulation were always

5. Davenport, C. B.: Body Build and Its Inheritance, publication 329, Carnegie Institute of Washington, 1923. McLester, J. S.: Nutrition and Diet in Health and Disease, Philadelphia, W. B. Saunders Company, 1939.

6. (*a*) Starr, Collins and Wood.[2a] (*b*) Starr, I.; Donal, J. S., Jr.; Margolies, A.; Collins, L. H., and Gamble, C. J.: Studies of the Heart and Circulation in Disease: Estimations of Basal Cardiac Output, Metabolism, Heart Size and

(Footnote continued on next page)

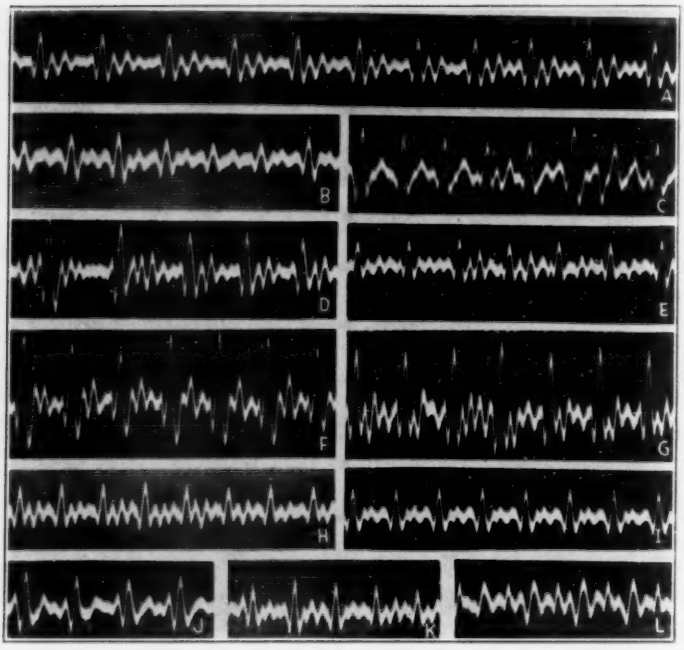


Fig. 1.—Ballistocardiograms (one-half actual size) of 1 normal subject and 9 patients with hyperkinemia. The time record at the top applies to all, the largest interval being one second. In comparing these records by inspection one must remember that, while the size of the major deflections is related to the absolute amount of the cardiac output, the decision concerning normality depends on this output related to the patient's weight. Also, allowance must be made for the subject's age, for older persons, even though healthy, tend to have smaller impacts than their juniors.

A, record of E. D., a woman aged 21, 5 feet 7 inches (170.2 cm.) in height and weighing 140 pounds (63.5 Kg.). A normal person, she had a circulation which did not deviate from the normal average.

B, record showing the effect of fever. The patient, R. B., a man aged 40, was 5 feet 5 inches (165.1 cm.) in height and weighed 135 pounds (61.2 Kg.). He had gonorrheal arthritis, his temperature being 98.4 F. His circulation deviated from the expected normal by + 17 per cent, the normal limits being ± 22 per cent. *C*, record of the same patient after he had received an injection of killed typhoid bacilli. His temperature was 103.2 F. His circulation was + 79 per cent.

(Legend continued on next page)

Blood Pressure in Two Hundred and Thirty-Five Subjects, J. Clin. Investigation **13**:561-592 (July) 1934. (*c*) Starr, I.; Gamble, C. J.; Margolies, A.; Donal, J. S., Jr.; Joseph, N. R., and Eagle, E.: A Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work and Size: On Respiration, on Metabolic Rate, and on the Electrocardiogram, ibid. **16**:799-823 (Sept.) 1937.

EXPLANATION OF FIGURE 1—CONTINUED

D, record of E. K., a boy aged 14, 5 feet 3 inches (160 cm.) in height and weighing 91 pounds (41.3 Kg.). The systolic blood pressure was 130, and the sounds could be heard at zero pressure. There was clinical evidence of patency of the ductus arteriosus. Our estimate of the amount of the circulation was handicapped by lack of data on the aortic size in children, but the impacts were much larger than we have ever seen in boys of similar age and weight. *E*, record of the same boy seven weeks after successful ligation of the ductus by Dr. John B. Flick at the Pennsylvania Hospital. The blood pressure was 106 systolic and 65 diastolic in millimeters of mercury. The diastolic murmur had disappeared, and the circulation had diminished by 24 per cent.

F, record of J. D., a man aged 25, 5 feet 11 inches (180.3 cm.) in height and weighing 148 pounds (67.1 Kg.). The basal metabolic rate was + 14 per cent and the circulation + 57 per cent. This patient, with essential hyperkinemia, is further described in the text (case 6).

G, record of H. W., a man of 36, 5 feet 6 inches (167.6 cm.) in height and weighing 112 pounds (50.8 Kg.). There was thyrotoxicosis with a diffuse goiter. The basal metabolic rate was obtained with much difficulty, the patient not tolerating the mouth piece well. Repeated attempts were made; the lowest value believed possible was + 66 per cent. The circulation was + 109 per cent.

H, record of A. K., a woman of 18, 5 feet 5 inches (165.1 cm.) in height, who came to the hospital weighing 71 pounds (32.2 Kg.). There was anorexia nervosa. On admission she was weak. The circulation did not deviate from the normal in relation to her weight at that time. The basal metabolic rate was — 27 per cent. After forced feeding for three weeks she had gained 11 pounds (5 Kg.) and had become much stronger; the record shown was taken at that time. The circulation was + 52 per cent if related to her actual weight, but only + 4 per cent when related to her ideal weight, 120 pounds (54.4 Kg.). As she further improved the circulation returned to normal.

I, record of S. P., a woman of 27, 5 feet 3 inches (160 cm.) in height and weighing 101¼ pounds (45.9 Kg.). The basal metabolic rate was — 2 per cent and the circulation + 35 per cent. This case of essential hyperkinemia is further described in the text (case 7).

J, record of A. T., a man aged 33, 5 feet 6 inches (167.6 cm.) in height and weighing 121 pounds (54.9 Kg.). Repeated estimations of the basal metabolic rate gave normal results; the circulation was + 57 per cent. This case is further described in the text (case 1).

K, record of V. D., a woman of 41, 5 feet (152.4 cm.) tall and weighing 100 pounds (45.4 Kg.). Three months before the test the entire right lung had been removed by Dr. Julian Johnson because of lung abscess. A thoracoplasty had been performed two weeks before. There was no fever; the pulse rate was 118. The circulation was calculated to be + 66 per cent, but because of the displacement of the heart it was probably somewhat larger.

L, record of M. N., a man aged 47, 5 feet 7 inches (170.1 cm.) in height and weighing 160 pounds (72.6 Kg.). The blood pressure was 115 systolic and 92 diastolic. Six months before the test the entire left lung had been removed because of carcinoma by Dr. Julian Johnson. While the patient was convalescent from the operation the pulse rate was 125 and the form of the ballistocardiogram somewhat abnormal. At that time the circulation was calculated to exceed + 80 per cent. When the present record was taken the form had returned to normal during systole but an abnormal impact was present in diastole. The circulation exceeded + 30 per cent.

supervised by Starr, and those of basal metabolic rate have been performed since 1936 by Jonas. Members of the Robinette Foundation, especially Drs. M. M. Livezey, J. Edeikin and W. A. Jeffers, made and interpreted the electrocardiograms and orthodiagrams which we have used.

Source of Cases.—Most subjects were resident patients or outpatients at the Hospital of the University of Pennsylvania; 2 were from the Pennsylvania Hospital. Rare instances of supernormal circulation were found among about 400 healthy persons: medical students, physicians and hospital technicians tested during various investigations and class demonstrations.

Not all types of patients have been studied. Those too ill to be moved were not tested. We have had a limited experience with the acute febrile diseases, partly because our clinic contains few patients with such diseases and partly because precautions against infection made it more difficult to test them. When working with the ethyl iodide method, we distrusted the results in cases in which the lungs were abnormal and avoided such cases. In cases in which blood regurgitates through leaking heart valves, the ballistocardiogram indicates the total cardiac output rather than the amount which contributes to the circulation; so we have omitted such cases from this series. In extreme tachycardia the ballistic after-vibrations may interfere with the record of the following systole. When this occurred the case was omitted. With these exceptions our cases represent a fair cross section of the population of the medical ward with symptoms referred to the heart or the circulation, with the addition of certain interesting cases selected from the surgical wards.

Terminology.—The term "cardiac output" has always been employed to mean the output from one side of the heart. With reference to the normal state and to most conditions of disease this term is perfectly satisfactory, for the blood expelled from each side of the heart equals the amount of the systemic and also the pulmonary circulation. Therefore the gas methods, which measure the blood flow through the lungs, and the ballistocardiogram, which is chiefly influenced by movement in the aorta, should yield the same result, and both have the right to call their result the cardiac output.

But in certain clinical conditions this agreement does not hold. For example, in aortic regurgitation, the left cardiac output exceeds the right; only the latter equals the systemic and the pulmonary circulations. In patent ductus arteriosus the situation is even more confused; the left cardiac output is larger than the right, but the pulmonary circulation is larger than the systemic, for the left cardiac output equals, not the systemic, but the pulmonary circulation, while it is the right cardiac output which equals the systemic circulation. To use the term

"cardiac output" under such conditions without explanation is to invite confusion of thought.

Therefore we prefer to emphasize the "amount of the circulation," by which we mean the systemic circulation. This term permits no confusion throughout the clinical field, and it places the emphasis on the amount of blood available to supply the needs of the body organs.

In a previous communication we used the term "subnormal circulation" to indicate circulation below the lower normal limit. This term seemed perfectly satisfactory, but the corresponding term, "supernormal circulation," is more awkward, and the adjective form, as in "supernormal circulatory state," is even worse. The discovery of a more satisfactory term was not easy. "Supercirculation" smacks unpleasantly of Hollywood, while "hypercirculation," of mixed parentage, derives dignity only from association with its half-brother, "hypertension," which has certainly made its place in the English language in spite of carrying a bar sinister. Among the derivations from Greek roots, "hyperrheaemia" requires too much effort to pronounce differently from the familiar, and very different, "hyperemia." "Hyperkinemia," easy to pronounce and with an even shorter adjective, is the best term we have found; Dr. J. H. Austin suggested it.

We propose, therefore, to use the terms hyperkinemia and hypokinemia to indicate the corresponding abnormalities in the amount of the systemic circulation of resting subjects.

RESULTS

Patients with Hyperkinemia Considered as a Group.—Sex: Of the patients, 57 were males and 43 were females. The small disproportion is probably due to two facts. One of us (I. S.) selected the patients for study, and in recent years his terms of service in the men's ward have exceeded those in the women's ward. Also, he preferred to study the patients of whom he was in charge.

Age: The distribution of the group is shown in figure 2. The subjects tended to be somewhat younger than those with hypokinemia,[1] but the range spread throughout life.

Habitus: There is a distinct tendency for patients with hyperkinemia to be underweight. The deviation from the ideal weight, a figure calculated from acturial data and based on the subject's age and height, is given in figure 2. Only 20 of the 100 patients were over their ideal weight. Patients from 21 to 25 pounds (from 9 to 11 Kg.) underweight were found with the greatest frequency.

History: The histories gave no positive information which would enable one to suspect hyperkinemia. As might have been expected from common experience with the increased circulation present during exercise or excitement, palpitation was the group's most common symp-

tom, but for only 31 patients was it recorded as abnormal. Found so frequently in patients without increased circulation who suffer from hypertension or cardiac disease, and also occasionally in healthy young adults, this symptom is of little help in identifying the magnitude of the circulation.

We also studied the frequency of excessive dyspnea on exertion, weakness, nervousness and tremor. When present these symptoms

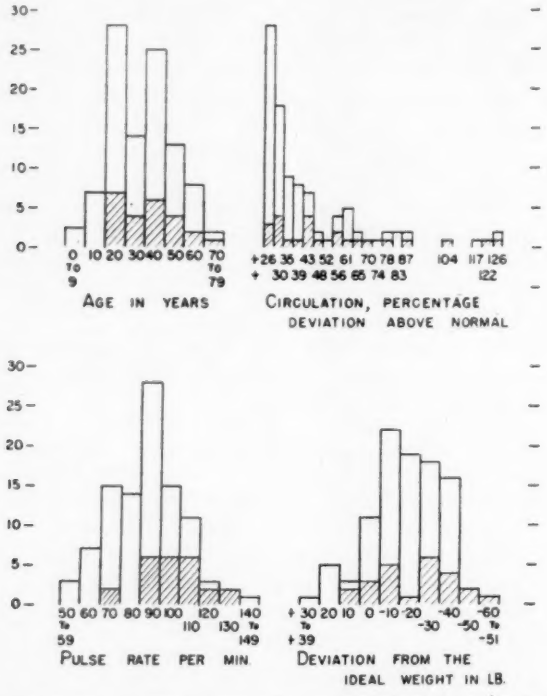


Fig. 2.—Frequency diagram from data on patients with hyperkinemia. The cross-hatched areas indicate data obtained from the patients with hyperthyroidism in our series.

could usually be accounted for by the major disease from which the patient suffered, and we found no reason to consider them characteristic of hyperkinemia.

Physical Examination: This likewise gave no conclusive evidence of the condition. Our data on the pulse rate are given in figure 2, where it will be seen that there was a tendency for the rate to be high, values in the 90's being found most frequently. But hyperkinemia may be present with either tachycardia or bradycardia.

The pulse volume, in reality a pressure difference unrelated to blood flow, showed nothing characteristic.

The blood pressure was normal in the great majority of the patients. A few in the series had true hypertension, and a large pulse pressure was found in patients with arteriovenous communications and in some with hyperthyroidism. These were the only abnormalities found.

Special Tests: Electrocardiograms, estimations of basal metabolic rate and fluoroscopic examinations of the heart were made for many patients. Abnormalities were encountered in some patients, but they were always characteristic of the primary disease, such as advanced heart disease or thyrotoxicosis; so these results will be discussed in connection with the appropriate subgroups. In other patients these

TABLE 1.—*Clinical Classification and Frequency of Hyperkinemia*

Group	Total Number of Patients Tested	Number with Hyperkinemia	Percentage with Hyperkinemia
Healthy persons	400	16	4
Patients with hyperthyroidism without obvious cardiac involvement	27	24	80
Patients with emaciation without disease of heart or circulation	12	9	75
Patients with abnormal intercirculatory communications			
Patent ductus arteriosus	7	6	86
Peripheral arteriovenous communications	4	1	25
Patients with anemia	21	5	24
Patients with febrile disease	8	1	12
Patients with hypertension	150	6	4
Patients with pulmonary conditions			
Postpneumonectomy	5	4	80
Pulmonary disease	12	3	25
Patients with other conditions (miscellaneous group)	Approximately 900	7	1
Patients with essential hyperkinemia	..	17	..

tests gave normal results, and we found nothing characteristic of hyperkinemia itself.

In short, besides the knowledge that hyperkinemia is likely to occur in persons who are underweight and have some elevation of the resting pulse rate, nothing has been discovered which permits one to identify it from the history, the physical examination or routine laboratory tests.

The Subdivisions of Hyperkinemia.—Table 1 shows our patients with hyperkinemia subdivided according to diagnosis. It also shows the proportion of such patients to the total number of similar subjects we have examined. Some comment is necessary.

Hyperkinemia is found occasionally in healthy persons. Sometimes it was discovered in class demonstrations and was undoubtedly due to excitement, but in large part its observation is to be attributed to an accidental summation of errors. In work with methods which contain

errors there will always be some overlapping of normal and abnormal groups.

Almost all of our patients with hyperthyroidism without evident cardiac involvement had hyperkinemia, and the presence of this abnormality has been reported frequently.[7]

The emaciated subgroup contained 4 young women in whom no organic abnormality was demonstrated by the hospital study, and their data are given in table 2. The other 5 emaciated patients showing

TABLE 2.—*Amount of the Circulation Related to Actual Weight of 4 Young Women with Anorexia Nervosa*

Patient, Age and Height	Date	Weight, Pounds	Blood Pressure, Mm. of Mercury	Circulation, Percentage from Normal	Pulse Rate	Basal Metabolic Rate, Percentage from Normal	Comment
A. K.; 17; 5′ 7″	10/21	71	90/64	0	77	−27	Patient very weak; hemoglobin content 84%
	10/23	..	.....	....	...	−23	
	11/14	82	110/60	+52	108	....	Much stronger
	11/21	..	.....	....	...	− 5	
	11/22	88	110/60	+ 4	98	....	Anemic; hemoglobin content 56%
	4/11	73	108/60	−17	62	....	Second admission
M. B.; 20; 5′ ½″	3/21	..	.....	....	..	+ 8	
	3/26	74	120/70	+39	98		
	3/28	..	.....	....	..	− 8	
H. P.; 21; 5′ 4″	4/22	93	112/72	+43	100	−14	
R. B.; 22; 5′ 2″	11/ 1	..	.....	....	..	−40	
	11/ 7	57	80/58	+26	63		
	11/15	60	78/54	+ 9	65		
	12/ 9	..	.....	....	..	−18	
	12/16	..	.....	....	..	−18	
	12/24	75	86/60	− 9	58		
	1/ 3	..	.....	....	..	−25	

hyperkinemia had lost from 42 to 22 pounds (19 to 10 Kg.) because of peptic ulcer or prolonged infectious disease.

However, not all emaciated patients show hyperkinemia. We have records of 6 such patients in whom its absence could be attributed to

7. (*a*) Liljestrand, G., and Stenström, N.: Clinical Studies on the Work of Heart During Rest: I. Blood Flow and Blood Pressure in Exophthalmic Goiter, Acta med. Scandinav. **63**:99-129, 1925. (*b*) Fullerton, C. W., and Harrop, G. A., Jr.: The Cardiac Output in Hyperthyroidism, Bull. Johns Hopkins Hosp. **46**:203-216 (Feb.) 1930. (*c*) Boothby, W., and Rynearson, C. H.: Increase in Circulation Rate Produced by Exophthalmic Goiter, Arch. Int. Med. **55**:547-557 (April) 1935. (*d*) Lequime, J.: Le débit cardiaque, études expérimentales et cliniques, Paris, Masson & Cie, 1940.

advanced heart disease or hypertension. But there were 3 other patients, 48, 35 and 27 pounds (22, 16 and 12 Kg.) underweight, who had normal circulation without any obvious reason. Indeed, the diagnosis of hyperkinemia in the presence of emaciation is largely a matter of definition, and this fact has been discussed.

Attention was directed to the subgroup with pulmonary disease by the finding of hyperkinemia in 4 of 5 patients tested from two weeks to six months after the surgical removal of one lung. These patients had resting pulse rates of 125, 118, 112 and 95. The presence of pronounced cardiac displacement would cause an error in estimating the circulation by ballistocardiogram, but its direction indicates that the circulation was even larger than our estimate of it.

In other patients with pulmonary disease, hyperkinemia has been found infrequently. Most patients with advanced diffuse pulmonary fibrosis from silicosis or infection have had normal or subnormal circulation.

In association with hypertension, hyperkinemia has been found only rarely, but the 6 patients with this combination had a great deal in common. One had glomerulonephritis and the other 5 essential hypertension. The highest blood pressure was 250 systolic and 137 diastolic and the lowest 156 systolic and 112 diastolic. All but 1 had great cardiac enlargement, the silhouette areas ranging from + 118 to + 47 per cent from the expected normal, while the heart of the last was top normal in size. All these patients were extremely ill and suffering from cardiac or cerebral manifestations. Three died within a month, and the remainder were discharged in such poor condition that prolonged life seemed most unlikely. Apparently hyperkinemia is found associated with hypertension only as a terminal condition; so we have no evidence that the increased circulation is a factor in the genesis of hypertension.

When patients with abnormal intercirculatory communications are studied there are errors in estimating cardiac output by any method.[8] The ballistocardiogram overestimates the amount of the circulation in this condition, but theoretic considerations led to the expectation that the error would be too small to account for the large abnormalities found in most of these patients.

Some of our patients in this subgroup were children, and special difficulties affected the interpretation of results. The lack of data on aortic size in children prevents estimation of the absolute amount of circulation but does not hinder the detection of changes in individual patients. Also, we have tested few normal children. But the children included in this study gave impacts so much larger than healthy controls

8. Keys, A.: Estimation by the Foreign Gas Method of the Net (Systemic) Cardiac Output in Conditions Where There Is Recirculation Through the Lungs, Am. J. Physiol. **134**:268-280 (Sept.) 1941.

that we have not hesitated to include them among the subjects with hyperkinemia.

Of the 8 patients with hyperkinemia in this subgroup, in 6 there was patent ductus arteriosus, the diagnosis being proved at operation for 5. In 1 of the remainder there was a traumatic arteriovenous communication of the occiput; in the other, an interventricular septal defect, demonstrated much later at necropsy. The 4 patients without hyperkinemia included 1 with patent ductus arteriosus proved at an operation which he did not survive. In 2 there was a traumatic arteriovenous communication in the leg and in 1 a congenital hemangioma of the leg. In the last 3 patients small changes in blood pressure, pulse and circulation on occlusion of the vessels of the affected leg indicated that the communications were small ones.

After ligation of the ductus the change in the circulation was usually striking. The records of 1 patient are shown in figure 1. In addition, in an adult operated on by Dr. John B. Flick, the circulation diminished from + 65 to + 4 per cent. In 3 children operated on by Dr. Julian Johnson, it diminished by 35, 24 and 10 per cent, respectively. These results are similar to those of Eppinger, Burwell and Gross.[9]

The infrequency of hyperkinemia in association with the febrile diseases was unexpected. Although an increase in the circulation after the artificial induction of fever has been demonstrated repeatedly[10] (an example is shown in figure 1), we found hyperkinemia in only 1 of 8 patients tested during a febrile disease. This patient had a temperature of 100.6 F. from phlebitis. In 7 other patients with the temperature between 101 and 104 F., tested during typhoid fever, lobar pneumonia, rheumatic fever or tuberculosis, normal circulation was found. Our data are few, but they suggest that hyperkinemia will be found in the sthenic, not in the asthenic, phase of the febrile diseases. Perhaps these findings are a demonstration of the old view which recognized a difference between the circulation in the sthenic and the asthenic stages of fever and served as the basis for such practices as bleeding early, but never late, in the course.

Also, among patients with anemia the number with hyperkinemia was smaller than the literature had led us to expect.[11] In each of 5

9. Eppinger, E. C.; Burwell, C. S., and Gross, R. E.: The Effects of Patent Ductus Arteriosus on the Circulation, J. Clin. Investigation **20**:127-144 (March) 1941.

10. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

11. Liljestrand, G., and Stenström, N.: Clinical Studies on the Work of the Heart During Rest: II. The Influence of Variation in the Hemoglobin Content in the Blood Flow, Acta med. Scandinav. **63**:130-141, 1925. Dautrebande, L.: Le débit cardiaque dans l'anémie, Compt. rend. Soc. de biol. **93**:1029-1031 (Oct.) 1925. Pellegrini, G.: Portata cardiaca e gittata pulsatona negli anemici e modificazioni di esse dopo transfusione di sangue, Boll. d. Soc. med-chir., Pavia. **48**:611 and 673, 1934.

patients tested twice, the circulation diminished as the hemoglobin increased, a fact suggesting that acceleration of the circulation was compensating for the hemoglobin deficiency. But when the results in table 3 are inspected it is evident that most anemic patients do not have hyperkinemia and that circulatory compensation must be a minor factor in most cases.

The miscellaneous subgroup consisted of 7 persons each suffering from a different disease. Since excitement may cause hyperkinemia in any one, their cases deserve no discussion.

TABLE 3.—*Relation of Circulation to Hemoglobin Content in Anemia*

Date	Subject	Age, Yr.	Hemoglobin Content, Percentage	Red Blood Cells	Circulation per Minute per Pound of Body Weight, Percentage Deviation from Normal	Pulse Rate	Diagnosis
2/ 4/39	S. C.	18	64	3,700,000	+30	86	Purpura (capillary toxicosis)
10/30/39	C. Z.	35	65	3,600,000	—17	78	Biliary cirrhosis of liver
2/ 7/39	U. S.	69	61	2,700,000	—13	72	Arteriosclerosis, hypertension, cirrhosis of liver
1/ 1/36	F. M.	59	58	2,600,000	+28	98	Primary pernicious anemia
11/22/39	K. F.	18	53	2,500,000	—26	69	Aplastic anemia
11/28/41	R. S.	27	52	3,800,000	—13	72	Iron deficiency anemia
11/29/39	J. M.	55	50	2,600,000	+48	90	Secondary anemia; ? cause
12/21/39	A. P.	21	50	3,900,000	— 4	82	Subacute glomerulonephritis
2/28/40	A. P.	..	61	3,500,000	—22	92	Subacute glomerulonephritis
10/28/37	C. K.	59	48	2,800,000	+13	85	Duodenal ulcer; hemorrhage
9/18/39	E. G.	18	45	2,200,000	0	95	Chronic anemia (unclassified)
9/18/37	J. Q.	56	40	1,600,000	+17	101	Primary pernicious anemia
11/29/37	T. R.	59	38	2,000,000	— 9	68	Duodenal ulcer; hemorrhage
11/ 8/40	F. H.	50	37	2,700,000	+24	84	Bleeding hemorrhoids
1/ 2/37	O. P.	43	37	2,000,000	+55	84	Duodenal ulcer; hemorrhage
10/30/39	C. K.	37	35	1,700,000	+ 9	120	Duodenal ulcer; hemorrhage
5/13/38	H. C.	58	34	1,200,000	+ 9	70	Primary pernicious anemia
5/20/38	H. C.	..	57	2,300,000	—13	48	Primary pernicious anemia
1/31/40	E. D.	26	28	2,600,000	—22	84	Idiopathic hypochromic anemia
2/13/40	E. D.	..	67	3,600,000	—39	67	Idiopathic hypochromic anemia
1/12/38	M. K.	34	22	2,400,000	+22	100	Idiopathic microcytic anemia
1/29/38	M. K.	..	67	4,000,000	+ 4	62	Idiopathic microcytic anemia
12/18/39	E. H.	17	20	2,600,000	+ 4	94	Chlorosis
1/17/40	E. H.	..	67	.....	—26	90	Chlorosis

The remaining subgroup, having the condition we have called essential hyperkinemia, is especially interesting, because this finding throws new light on hyperkinemia. We have studied 17 patients with essential hyperkinemia, chiefly young adults of both sexes.

Their symptoms were always mild. All denied weakness, although several admitted that they tired easily. Thirteen thought of themselves as nervous. Seven when questioned closely admitted dizziness on change of position, usually immediately after arising but often on bending over and sometimes when lying down. This was never a major complaint, and only 1 patient had ever fainted, and she only once. Five

thought they had undue dyspnea on exertion; in 6, palpitation was judged to be excessive. Two complained of attacks of indefinite precordial pain not related to exercise.

Examination disclosed that they were usually underweight; none was over his ideal weight, and the average was 14 pounds (6.4 Kg.) under this figure. The pulse rate tended to be a little rapid, averaging 91. After a rest of fifteen minutes, the pulse rate was still over 100 in 5 subjects, but it was under 75 in 3. The thyroid was palpable in 5 patients. Excessive tremor of the extended hands was noted in 6.

The blood pressure was never elevated, averaging 124 systolic and 75 diastolic. The basal metabolic rate was always within normal limits, averaging — 2 per cent. In contrast, the circulation averaged 35 per cent over the expected normal. Routine blood counts and urinalyses revealed nothing abnormal, and electrocardiograms, secured in 10 cases, showed nothing of importance.

A number of brief case reports will serve to acquaint readers with the outstanding features of these cases (the records of several are shown in figure 1):

Case 1.—A. T., a man aged 33 years, was 5 feet 6 inches (167.6 cm.) tall and weighed 121½ pounds (55.1 Kg.). During the preceding twenty years he had had repeated admissions and operations for chronic osteomyelitis of the left femur and the right tibia, and the wounds had continued to drain a little. Nervousness was first noted one year before. Since then there had been palpitation on exertion and excitement and more dyspnea on exertion than formerly.

Physical examination disclosed slight exophthalmos, slight diffuse thyroid enlargement, slight tremor of the extended hands and draining scars at the right knee and in the left inguinal region. The pulse rate varied between 75 and 105. The patient was afebrile.

Every examiner agreed with the tentative diagnosis of hyperthyroidism, but basal metabolic rates determined in two laboratories were — 9, — 9, — 19 and — 6 per cent. The circulation was + 57 per cent and the pulse rate 96. An electrocardiogram was normal.

Case 2.—W. T., a man aged 50 years, an electrician, was 5 feet 8 inches (172.7 cm.) tall and weighed 126 pounds (57.2 Kg.). He complained of a tired feeling, a lack of appetite, constipation and dizziness on suddenly arising to his feet. He had lost 25 pounds (11.3 Kg.) over a period of years.

Physical examination disclosed a relaxed abdominal wall and a low blood pressure, generally under 90 systolic and 65 diastolic. There was no tachycardia. The tentative diagnosis was hyperthyroidism, but the basal metabolic rate was — 10 per cent. The circulation was just above the upper normal limit; the pulse rate was 70.

An abdominal binder alleviated many of his symptoms.

Case 3.—C. A., a man aged 29 years, a janitor, was 5 feet 7 inches (170.2 cm.) tall and weighed 137 pounds (62.1 Kg.). For the past year he had complained of nervousness, burning of the eyes, headache, loss of energy and rapid heart action. His doctor had diagnosed thyrotoxicosis and sent him to the surgical service for thyroidectomy.

Physical examination showed a slightly enlarged soft thyroid. Two estimates of the basal metabolic rate gave results of + 7 and — 7 per cent. The circulation was + 30 per cent and the pulse rate 110.

CASE 4.—J. R., a man aged 32, a clerk, was 5 feet 7 inches (170.2 cm.) tall and weighed 125 pounds (56.7 Kg.). For the past year he had suffered from attacks of precordial distress accompanied by weakness, faintness, a sensation of epigastric fulness, belching and pain on the medial side of the left arm. These attacks occurred after eating, not after exercise. There was also epigastric "burning" relieved by food. Angina pectoris had been diagnosed by the attending physician, certainly on insufficient grounds.

Physical examination showed nothing abnormal. Gastrointestinal roentgen examination gave negative results. An electrocardiogram showed a slight abnormality attributed to the digitalis the patient had received before admission. The basal metabolic rate was —16 per cent, the circulation was + 30 per cent and the pulse rate was 59.

CASE 5.—A. T., a man aged 42 years, a riveter, was 6 feet (182.9 cm.) tall and weighed 170 pounds (77.1 Kg.). Palpitations and a cardiac irregularity had worried him for the past two years, and his worry increased until he was unable to sleep. He also suffered from Raynaud's syndrome in his hands, probably secondary to his occupation.

Physical examination revealed a look of apprehension. The thyroid was diffusely enlarged. There were occasional ventricular extrasystoles. The basal metabolic rate was —17 and —13 per cent. The circulation was + 26 per cent and the pulse rate 90.

A psychiatric consultant unearthed a history of insecurity caused by a quarrel with his boss and believed the resulting anxiety was sufficient to account for the symptoms.

CASE 6.—J. D., a man aged 25 years, a hospital employee, was 5 feet 11 inches (180.3 cm.) tall and weighed 148 pounds (67.1 Kg.). For the past year he had suffered from spells of dizziness, which usually, but not always, occurred when he stood erect. Other complaints were nervousness and substernal pain not related to exercise. All these were mild, and it was acute diarrhea which first brought him to the dispensary.

Physical examination showed nothing abnormal except constant fidgeting. The basal metabolic rate was + 14 per cent. The circulation was + 57 per cent on the first test and + 35 per cent two months later, the pulse rate being 90 and 74, respectively.

CASE 7.—S. P., a woman aged 27, a housewife, was 5 feet 3 inches (160 cm.) tall and weighed 101½ pounds (46 Kg.). Tachycardia was always the outstanding feature of this case; it had been present for many years and was accompanied by few symptoms. Nevertheless, the thyroid having been palpable, a partial thyroidectomy had been performed three years before, without any improvement. When examined the patient insisted she was well and went to physicians only to allay the fears of her husband. She acknowledged that she tired easily. Palpitation was noted only after exercise.

Physical examination showed nothing abnormal except tachycardia, the rate being 104 after fifteen minutes of rest. The basal metabolic rate was —2 per cent and the circulation + 35 per cent.

Evidently besides the hyperkinemia, the feature common to the great majority of the patients in this subgroup was a close resemblance of their symptoms to those of thyrotoxicosis in spite of a normal basal metabolic rate.

COMMENT

Any study of clinical hyperkinemia is complicated by a factor not present when hypokinemia is investigated. Hyperkinemia may be readily induced in any subject by drugs such as epinephrine and amyl nitrite and their allies or by excitement. Emotion is so hard to produce experimentally that the accidental demonstration of a striking emotional effect deserves special mention.

CASE 8.—E. T., a woman of 54 years, was known to have had hypertension for six years. She also had a uterine fibroid tumor which was large enough to encroach on the capacity of the bladder and lead to occasional incontinence.

In a routine study of the circulation in hypertension, the first of projected duplicate estimations by the ethyl iodide method had been completed uneventfully when incontinence supervened to the great annoyance and embarrassment of the patient. Nevertheless, she gamely continued to breathe through the apparatus while the operators, realizing that something had happened but ignorant of what it was, continued to take samples and make observations. Before the accident the results showed nothing abnormal except the blood pressure. After it, the emotional tension increased the cardiac output by 85 per cent, the pulse rate by 37 per cent, the volume of respiration by 89 per cent and the oxygen consumption by 77 per cent, while the blood pressure changed from 220 systolic and 120 diastolic to 260 systolic and 152 diastolic in millimeters of mercury.

Therefore hyperkinemia may indicate an emotional state as well as a primary physiologic condition. Only when it is found repeatedly in an individual patient or in a group of similar patients can it be taken as indicating the latter. The finding of it occasionally in association with any diseased condition is to be expected and deserves no emphasis.

The data in this paper, together with those published before,[1] permit certain generalizations which deserve discussion. It is evident that in many of the instances in which it is encountered in disease, hyperkinemia may serve a useful purpose. In hyperthyroidism and fever it meets the demands of increased tissue metabolism. In pulmonary disease and anemia it aids in overcoming a handicap which threatens to deprive the tissues of their normal supply of oxygen. In the case of abnormal intercirculatory communications it maintains the blood supply to the vital organs in spite of the tendency of the communication to draw blood from them. When found in advanced hypertensive cardiovascular disease it may represent a final attempt on the part of the body to maintain the blood supply of diseased organs, such as the kidneys. Only in essential hyperkinemia is one left without any clear idea of either the purpose or the causation of the abnormality. In this connection three questions present themselves.

The first question concerns the relationship of essential hyperkinemia to the neuroses. Are the subjects affected simply abnormally emotional persons who, confronted with the unusual situation inherent in making any test, react by the hyperkinemia of excitement? This

conception does not satisfactorily explain the findings. In the resident patients the pulse rates found at the time of our tests did not differ materially from those often found in the ward. Also, if excitement were the cause of the findings one would expect that the more arduous estimation of basal metabolic rate would produce enough emotion to increase that rate. Our patients had normal basal rates. So we do not think that emotion is the whole explanation of our findings, though we would be the last to deny that it might have influenced the results in some cases.

The second question concerns the relation of this type of hyperkinemia to the secretion of epinephrine or of sympathin. In some respects there are striking similarities between the clinical picture presented by our patients and that found in any normal subject after an injection of epinephrine. Hyperkinemia, tachycardia, tremor, apprehension, palpitation and sometimes dizziness irrespective of position are found in both. In several of our patients an injection of epinephrine chloride reproduced the subjective symptoms of which they commonly complained; Kessel and Hyman [12] made the same observation. But the differences are striking also. In essential hyperkinemia there is neither hypertension nor increased metabolic rate, which are regularly found after an injection of epinephrine chloride. To attribute essential hyperkinemia to an increased secretion of epinephrine would be unjustified in the light of present knowledge.

The third question is concerned with the relation of essential hyperkinemia to thryoid dysfunction. In spite of the normal basal metabolic rate found in all the patients with essential hyperkinemia, slight enlargement of the thyroid occurs far more frequently in such patients than in the general population. Certainly the superficial resemblance to patients with thyrotoxicosis is often striking. We have a point to add to the evidence for a relationship. In several of our cases of thyrotoxicosis, after partial thyroidectomy the metabolic rate has returned to normal before the circulation, leaving the patient temporarily in a condition indistinguishable from essential hyperkinemia (fig. 3*B*). This observation amplifies the well known fact that after this operation the metabolic rate often returns to normal before the pulse rate. The idea of multiple thyroid hormones is old,[13] and if one stimulated the circulation without stimulating the metabolic rate it would explain our findings. Nevertheless, 1 of our patients with essentail hyperkinemia underwent partial thyroidectomy, and 3 others had roentgen therapy to

12. Kessel, L., and Hyman, H. T.: Studies of Graves' Syndrome and the Involuntary Nervous System: II. The Clinical Manifestation of Disturbances of the Involuntary Nervous System (Autonomic Imbalance), Am. J. M. Sc. **165**: 513-530 (April) 1923.

13. Crotti, A.: Thyroid and Thymus, Philadelphia, Lea & Febiger, 1922.

the thyroid without any improvement. One patient has been followed for ten years, and thyrotoxicosis has not developed. Kessel and Hyman [12] have reported similar cases. If essential hyperkinemia should prove to be due to thyroid dysfunction, it is not the forme fruste of the older authors [13] but a different type from any now known.

Even if little conclusive can be said about causation, such patients will be familiar to every experienced clinician, for theirs are the cases in which the history, appearance and physical findings suggest hyperthyroidism although the basal metabolic rate is found to be normal. Cases which we believe to be similar have been studied in the army by Peabody, Wearn and Tompkins,[14] who called the condition "irritable heart," and in civil life by Kessel and Hyman,[12] who gave it the name of "autonomic imbalance." In 7 apparently similar cases, the trouble being called "prebasedow," the cardiac output was demonstrated to be above normal by Bansi,[15] and in 2 in which the diagnosis was "parabasedowism" or sympathicotonia, Lequime [7d] reported the same finding. All these terms imply more than is known, for the ultimate cause may be neither in the heart nor in the thyroid, and the trouble may be of humeral rather than of nervous origin. The term essential hyperkinemia is purely descriptive, admits ignorance of the fundamental causation and indicates the major physiologic abnormality.

The results suggest the reason why such cases are often confused with cases of hyperthyroidism. Hyperkinemia is common to both. A question immediately arises, Are not many of the manifestations of hyperthyroidism, so often recognized at a glance by experienced clinicians, due to the increased circulation rather than to anything more immediately associated with the metabolic rate? If this was true, patients with hyperthyroidism on showing cardiac complications would be expected to lose part of the characteristic manifestations. We are inclined to believe that this often happens, for we can think of a number of patients with cardiac complications whose hyperthyroidism went unrecognized for a long time because it occurred to no one to estimate the basal metabolic rate.

But we do not contend that all patients with hyperkinemia have an appearance which suggests the patient with hyperthyroidism. Some certainly have, and others have not; but additional factors present, such as anemia, pulmonary disease or other severe illnesses, may cause so

14. Peabody, W.; Wearn, J. T., and Tompkins, E. H.: Metabolism in Irritable Heart, M. Clin. North America **2**:507-515 (Sept.) 1918.

15. Bansi, H. W.: Kreislaufstudien beim Basedow und bei der Herz-neurose, Ztschr. f. klin. Med. **110**:633-684, 1929.

many signs and symptoms themselves that those due to hyperkinemia may not be apparent.

Figure 3 has been designed to show the relation between the circulation and the metabolic rate whenever one or both are abnormal, the data being derived from both this and previous papers.[16]

In figure 3 *A* are given the results obtained in cases of hyperthyroidism without valid evidence of cardiac involvement and in cases of

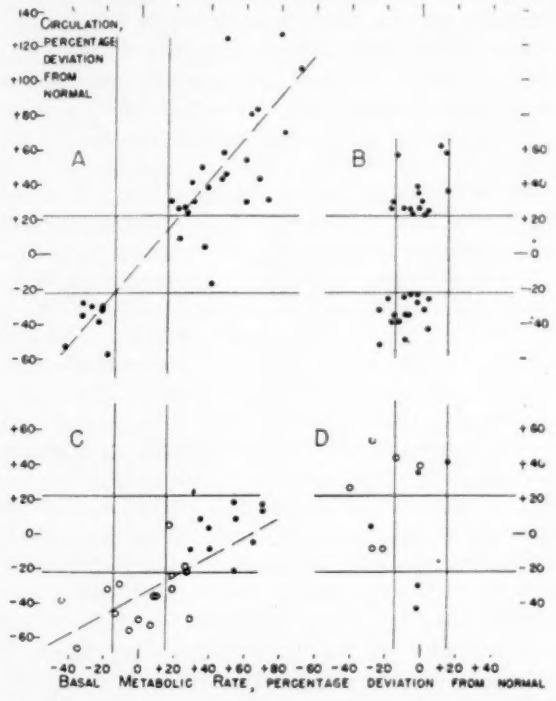


Fig. 3.—Graphs showing the relation between abnormalities of the circulation and the basal metabolic rate. The solid lines indicate the normal limits; so the enclosed rectangles define the area in which both circulation and metabolic rate were normal. *A*, data on patients with hyperthyroidism and hypothyroidism without known cardiac involvement. The broken line is the calculated line of best fit (regression, y on x). *B*, data on patients with essential hyperkinemia and hypokinemia. *C*, the dots represent the results for patients with hyperthyroidism giving evidence of cardiac complications. The circles represent the results for patients with serious cardiac disease who had recovered from congestive heart failure. *D*, the dots represent the results obtained for patients who had had hyperthyroidism treated by partial thyroidectomy. The circles indicate the results obtained for certain emaciated persons.

16. Starr and Jonas.[1] Starr and others.[6b]

hypothyroidism also. There is excellent correlation between the circulation and the metabolic rate in these cases; the coefficient is 0.84, any value over 0.28 being significant. Indeed, the line of best fit passes almost directly through the origin, and its slope is close to unity.

The relation of the circulation to the metabolic rate finds physiologic expression in the arteriovenous oxygen difference. This has been much studied in hyperthyroidism, some authors [17] finding a diminution on the average and others little change. Our results support the latter group, but it should be noted that the variation of results in individual cases is large; so we are not surprised at the divergence of the averages obtained.

In 13 of our patients the basal metabolic rate was elevated but the circulation was within normal limits. There is collateral evidence that all but 3 of these patients suffered from cardiac involvement. Four had definitely enlarged hearts as estimated by orthodiagram; in 4 others edema of the ankles was demonstrated on admission. Another suffered from attacks of auricular fibrillation. In still another the liver was 4 cm. below the costal margin at the time the circulation was within normal limits; after several days of rest in bed the liver diminished in size and the circulation was then found to be above normal. Of the remaining 3 patients, 1 suffered from multiple bony metastases from a carcinoma of the breast in addition to the thyrotoxicosis. The 2 remaining patients showed no positive collateral evidence of cardiac involvement, but 1 was extremely prostrated by her disease. Another patient with hyperthyroidism, severe cardiac insufficiency and normal circulation has been reported on by Lequime.[7d]

In figure 3 *C* are shown data on our 10 patients with thyrotoxicosis with evidence of cardiac involvement and also on a group of patients who had either recovered from congestive heart failure or shown evidence of severe cardiac disease.[6b] None were in failure when the test was made. It will be seen at once that there was a significant correlation between the circulation and the metabolic rate of all these patients, the coefficient being 0.69, whereas any value above 0.32 is significant. But one should note that these patients had smaller circulations in proportion to their metabolic rates than the patients without cardiac complications, whose data are shown in figure 3 *A*. In figure 3 *C* the line of best fit passes far below the origin and the slope is only about 0.5.

These statistics lead to the following conclusions: In the absence of cardiac disease abnormal increments or decrements of basal metabolic rate are accompanied, on the average, by corresponding percentage

17. Bansi, H. W., and Groscurth, G.: Die Kreislaufleistung beim Basedow und Myxödem, Ztschr. f. klin. Med. **116**:583-602, 1931. Goldbloom, A.: Clinical Studies of Circulatory Adjustments, Clinical Evaluation of Cardiac Output Studies, Internat. Clin. **3**:206-245 (Sept.) 1936. Footnote 7.

changes in the circulation. In the presence of cardiac disease the circulation is smaller than one would expect from the metabolic rate, and the deficit increases with each increment of metabolic rate. Therefore an increased metabolic rate without a corresponding increase in the circulation suggests cardiac disease. Also, the data provide a reason for the success of the old clinical practice of reducing the metabolic rate in cases of heart disease by such measures as rest, diet and use of sedatives, for when this rate is at a minimum the circulatory deficit is also at a minimum. A somewhat similar viewpoint provided the theoretic basis for Blumgart's [18] trials of thyroidectomy in cases of cardiac disease.

In figure 3 *B* have been placed the data obtained for the subgroups with what we have called essential hyperkinemia and hypokinemia. The former patients have been discussed in this and the latter in a previous publication.[1] A comparison of figure 3 *B* with figure 3 *C* discloses that the circulation and the metabolic rate in patients with essential hypokinemia are identical with those of patients suffering from organic heart disease. The two groups doubtless share the symptoms dependent on their common abnormality, and it is not surprising that when the relation was not understood such a term as functional heart disease was employed. It is a poor term because the hearts of patients with essential hypokinemia are normal by any test now known, and the trouble should be sought elsewhere in the circulation.

In figure 3 *D* are given data obtained for other conditions in which the relation between circulation and metabolism was abnormal. An abnormal relation has been found frequently in emaciation, the results suggesting that the basal metabolic rate may diminish, as it regularly does in starvation,[19] but the circulation may not accompany it downward. We have occasionally found this abnormality after partial thyroidectomy, the circulation being above normal in some cases and below it in others, as if the operation had interfered with the normal coordination of circulation and metabolism.

SUMMARY

In a total experience of about 1,400 estimations of cardiac output, 100 patients were encountered in whom the resting circulation was above

18. Blumgart, H. L.; Levine, S. A., and Berlin, D. D.: An Attempt to Reduce the Basal Metabolic Rate of Cardiacs by Subtotal Thyroidectomy, Arch. Int. Med. **51**:867-877 (June) 1933. Blumgart, H. L.; Riseman, J. E. F.; Davis, D., and Berlin, D. D.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, ibid. **52**:165-225 (Aug.) 1933.

19. Du Bois, E. F.: Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1936.

normal, a condition we have called hyperkinemia. These patients were usually underweight, and they tended to have resting pulse rates above normal.

Hyperkinemia was encountered in almost all patients with thyrotoxicosis without cardiac involvement and in most patients with patent ductus arteriosus. It was found often in patients with emaciation and less frequently in those with pulmonary abnormalities, fever, anemia, hypertension and peripheral arteriovenous communications.

In 17 patients, hyperkinemia was present without any complicating condition having been discovered. These patients with essential hyperkinemia resembled patients with thyrotoxicosis in appearance, but the basal metabolic rate was always normal. The clinical characteristics of this subgroup have been described in detail.

The relation between abnormalities of the circulation and the basal metabolic rate has been studied by statistical methods. In uncomplicated hyperthyroidism and hypothyroidism the relation is almost 1 to 1; i. e., on the average, an abnormal increment or decrement in the basal metabolic rate is accompanied by an equal percentage change in the circulation. In heart disease these two functions are related, but the relationship is more nearly 1 to 0.5. Under such conditions the circulation is less than normal for any given metabolic rate, and the higher the metabolic rate the greater is the circulatory deficit.

Other instances of deviation from the normal 1 to 1 relationship between circulation and metabolic rate have been found in cases of emaciation and in some cases of hyperthyroidism after partial thyroidectomy.

3400 Spruce Street.

255 South Seventeenth Street.

CHRONIC GASTRITIS SIMULATING GASTRIC CARCINOMA

REPORT OF FIVE CASES

EUGENE FREEDMAN, M.D.

PAUL M. GLENN, M.D.

AND

THOMAS C. LAIPPLY, M.D.

CLEVELAND

As a result of refinements in technic of roentgen examination of the stomach and the introduction of the flexible gastroscope, chronic gastritis has received renewed attention. Chronic gastritis is frequently a generalized involvement of the stomach, but often it can be of severe degree and localized in various parts of the stomach. While the roentgen appearance of generalized hypertrophic gastritis can often be recognized, the localized forms are frequently difficult to differentiate from carcinoma. Even gastroscopically the differentiation between a localized inflammatory infiltration and one which is neoplastic cannot always be made.

Brunn and Pearl [1] first called attention to the fact that a malignant lesion can be simulated by chronic hypertrophic gastritis. Subsequently, Konjetzny [2] and Schindler [3] reported similar instances. In the past three years we have encountered 5 cases in which the roentgen and gastroscopic appearance of localized chronic hypertrophic gastritis simulated carcinoma of the stomach.

The difficulties in diagnosis presented by these cases were such that carcinoma could not be excluded before an exploratory laparotomy was done. In 3 of the cases the true nature of the lesion did not become apparent until histologic examination of the resected specimens was made.

From The University Hospitals and the Institute of Pathology, Western Reserve University.

1. Brunn, H., and Pearl, F.: Diffuse Gastric Polyposis, Adenopapillomatosis Gastrica, Surg., Gynec. & Obst. **43**:559 (Nov.) 1926.

2. Konjetzny, G. E.: Der Magenkrebs, Stuttgart, Ferdinand Enke, 1938; reviewed, J. A. M. A. **112**:1631 (April 22) 1939.

3. Schindler, R.: Gastritis Simulating Tumor Formation, Am. J. Digest. Dis. **6**:523 (Oct.) 1939.

REPORT OF CASES

CASE 1.—A 30 year old white male chemist complained of persistent epigastric pain of three weeks' duration. The pain had no relation to food or eating. He had no other complaints except that he had lost 20 pounds (9 Kg.) in weight. On physical examination he was undernourished and anemic, but otherwise normal. Laboratory examination of the blood yielded the following data: red cell count, 4,730,000; hemoglobin concentration, 45 per cent, and white cell count, 7,900. Gastric analysis showed a peak acidity of 8 units of free acid and 31 units of total acid. On examination the stool was strongly positive for occult blood. Clinically a lesion of the stomach was suspected and was thought to be a bleeding ulcer.

Roentgen examination (fig. 1 *a*) showed an irregular deformity of the distal end of the body of the stomach on the side of the greater curvature. The involved area measured about 8 cm. in length and 3.5 cm. in width. The rugae throughout

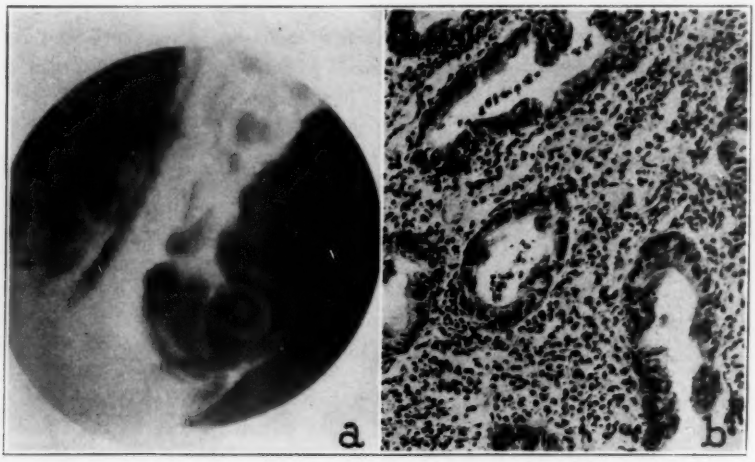


Fig. 1.—(*a*) A roentgenogram showing irregular contour and polypoid defects in the lumen on the side of the greater curvature of the body of the stomach. Note the normal rugae on the side of the lesser curvature. (*b*) A photomicrograph (× 130) showing lymphocytic infiltration of the gastric mucosa.

this area were markedly enlarged and distorted by several circular polypoid defects but were normal elsewhere. Peristalsis was absent in the involved portion. A diagnosis of carcinoma of the body of the stomach on the side of the greater curvature was made.

Gastroscopic examination revealed a normal antrum except for pallor of the mucous membrane. On the anterior wall 3 to 4 cm. above the antrum there was a distinct change in the appearance of the mucosa. There was a prominent, irregular, pale pinkish gray, nodular semicircular fold, which looked like the raised margin of a malignant ulcer. Proximal to this fold only small islands of irregular pale pink and hyperemic mucosa were visible in an otherwise homogeneous

surface covered with gelatinous greenish gray material. There was a suggestion of rugae extending through this region. These were thickened and irregular with multiple superficial hemorrhagic erosions. The lesion extended up to the fundus on the anterior wall and the greater curvature, but on the lesser curvature and the posterior aspect the mucosa showed only pallor and some irregularity of rugae. An infiltrative lesion involved the upper two thirds of the anterior wall and the greater curvature of the corpus of the stomach. The localization suggested that it was neoplastic, but the possibility of its being inflammatory could not be excluded.

At operation the stomach was found to be slightly dilated, the proximal half being paler than the distal portion. The wall of the corpus was distinctly lobulated and had a definite yellow color in contrast to the pink distal portion. On the surface of the body of the stomach there were numerous large dilated intercommunicating veins, which gave the serosa a mosaic pattern. Palpation revealed this portion of the stomach to be thicker than the rest. Exploration of the interior of the stomach revealed extensive redundancy and thickening of the mucosa and the submucosa.

Biopsy included a portion of the mucosa and the submucosa. Microscopic examination revealed a definite increase in the number of lymphocytes and plasma cells and also scattered polymorphonuclear neutrophilic leukocytes throughout the mucosal connective tissue (fig. 1 *b*). A regional lymph node was also removed which showed moderate diffuse hyperplasia of the reticular cells. These changes were indicative of acute and chronic gastritis and endothelial hyperplasia of the regional lymph node.

Case 2.—A 29 year old white man had for two years often vomited at night, the vomitus frequently containing clots of bright red blood. On an ulcer regimen the vomiting decreased. For six months he had dull, gnawing epigastric pain two to three hours after meals and at night, which was frequently relieved by taking alkali and milk. He had lost 20 pounds in weight. On physical examination he showed pallor and evidence of undernourishment. There was tenderness to palpation around the umbilicus and in the epigastrium. Laboratory examinations of the blood revealed a red cell count of 4,420,000, a hemoglobin concentration of 56 per cent and a white cell count of 8,000. Gastric analysis after stimulation with histamine failed to reveal any free acid. The total acid was 12 units. On examination the stools gave a strongly positive reaction for occult blood. Clinically, an ulcer with bleeding was suspected, though the anacidity was a disturbing factor.

Roentgen examination (fig. 2 *a*) revealed irregular defects of the contour in the cardiac portion of the stomach. These were most marked in the fundus, on the side of the greater curvature, there being only slight irregularity of the lesser curvature. In this region the rugae were distinctly widened. The pyloric portion was smooth in contour, and the rugae were of approximately normal width. The appearance suggested an infiltrating type of malignant tumor.

Gastroscopic examination was unsatisfactory. No contraction waves were noted in the antrum. In this region the mucosa had a distinctly granular surface with many pale pink, red and boggy gray areas. In many regions small amounts of adherent secretion and bright red blood were noted on the mucosal surface. Several

small hemorrhagic erosions were also noted. The corpus could not be seen because a considerable amount of blood-tinged fluid obscured vision.

At operation the stomach was found to be large. There were no palpable lymph nodes. On opening the stomach it was seen that throughout its proximal three fourths the mucosa was hyperemic, edematous and spongy. This abnormal mucosa ended abruptly in the prepyloric region where there were normal-looking gastric rugae. Gently wiping the abnormal mucosal surface readily produced bleeding.

Biopsy included mucosa and submucosa. The gastric glands were normal in number, elongated and tortuous, and some were distinctly dilated. Throughout the tunica propria there was an increase in the number of lymphoid and plasma cells, along with slight diffuse infiltration of polymorphonuclear leukocytes. The submucosa showed slight edema but no cellular infiltration (fig. 2 *b* and *c*). A diagnosis of acute and chronic gastritis was made.

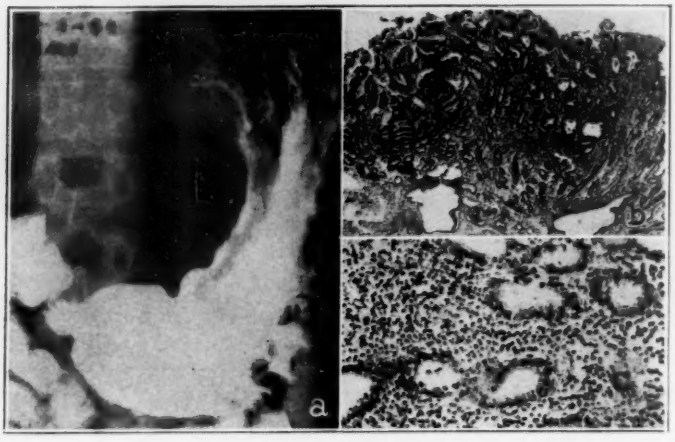


Fig. 2.—(*a*) A roentgenogram indicating the marked widening rugae in the cardiac portion of the stomach, irregularities of contour mainly on the side of the greater curvature and normal rugae in the pyloric portion. (*b*) A photomicrograph (× 45) illustrating elongation, tortuosity and dilatation of the gastric glands. (*c*) A photomicrograph (× 86) showing lymphocytic infiltration of the gastric mucosa.

Case 3.—A 50 year old white man complained of burning epigastric pain radiating under the sternum and anorexia of three months' duration. Food aggravated the pain; sodium bicarbonate relieved it. He had occasional vomiting and had lost 30 pounds (14 Kg.) in weight. On physical examination he was undernourished and had signs of mitral stenosis and insufficiency. The abdomen was normal. Laboratory examination of the blood revealed a red cell count of 4,190,000, a hemoglobin concentration of 90 per cent and a white cell count of 7,500. Gastric analysis showed peak acidity of 20 units of free acid and 33 units of total acid. On examination the stools did not show any occult blood. Clinical opinion was about equally divided between gastric ulcer and carcinoma.

Roentgen examination (fig. 3) revealed irregular contours of the cardiac end and the upper half of the body of the stomach, with various-sized oval and circular

defects within the lumen. The distal half of the stomach was normal. On account of our experience in several previous cases we thought that the changes were due to polypoid gastritis, although the possibility of polypoid carcinoma could not be excluded.

Gastroscopic examination showed the antrum and the pyloric canal to be normal and to function actively. A few centimeters proximal to the incisura on the anterior wall and the greater curvature there was much adherent greenish gray mucopurulent secretion. The mucosal surface was distinctly irregular because of many projecting rounded masses which appeared to be on the tops of large irregular nodular rugae. These protruding islands of mucosa showed many irregular areas of marked hyperemia, many petechiae and several small superficial erosions. On the lesser curvature and the posterior wall, the rugae appeared large and irregular and the mucosa had a mottled yellowish and greenish gray, roughly granular surface on which there were a few small hyperemic areas. In view of similar findings in a previous case the impression was that this was localized chronic hypertrophic gastritis.

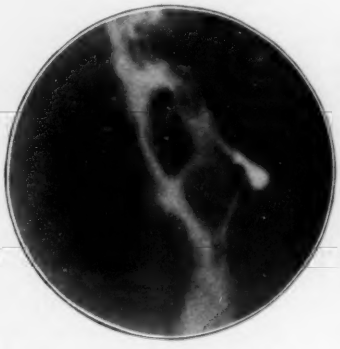


Fig. 3.—A spot roentgenogram of the cardiac end of the stomach, showing oval and circular defects within the lumen and irregularities of contour.

At operation the stomach was palpated and visualized up to the esophageal hiatus. It had a normal external appearance, and there were no palpable masses and there was no induration. There were no palpable lymph nodes in the gastrohepatic omentum and no peritoneal implants. The abdominal wall was closed without opening the stomach.

Case 4.—A 59 year old white woman had suffered attacks of indigestion for twenty years. These consisted of gnawing discomfort in the upper portion of the abdomen one hour after meals which was relieved by taking sodium bicarbonate dissolved in hot water. For five months she had had marked anorexia and fulness after little intake and had occasionally vomited. She had lost 30 pounds in two years. On physical examination she was emaciated and there was fulness in the left upper quadrant of the abdomen. Laboratory examination of the blood revealed a red cell count of 4,280,000, a hemoglobin concentration of 64 per cent and a white cell count of 8,100. Gastric analysis revealed a lack of free acid and 40 units of total acid after stimulation with histamine. On examination the stools were positive for occult blood. Clinically, a chronic peptic ulcer with pyloric obstruction and gastric carcinoma were considered.

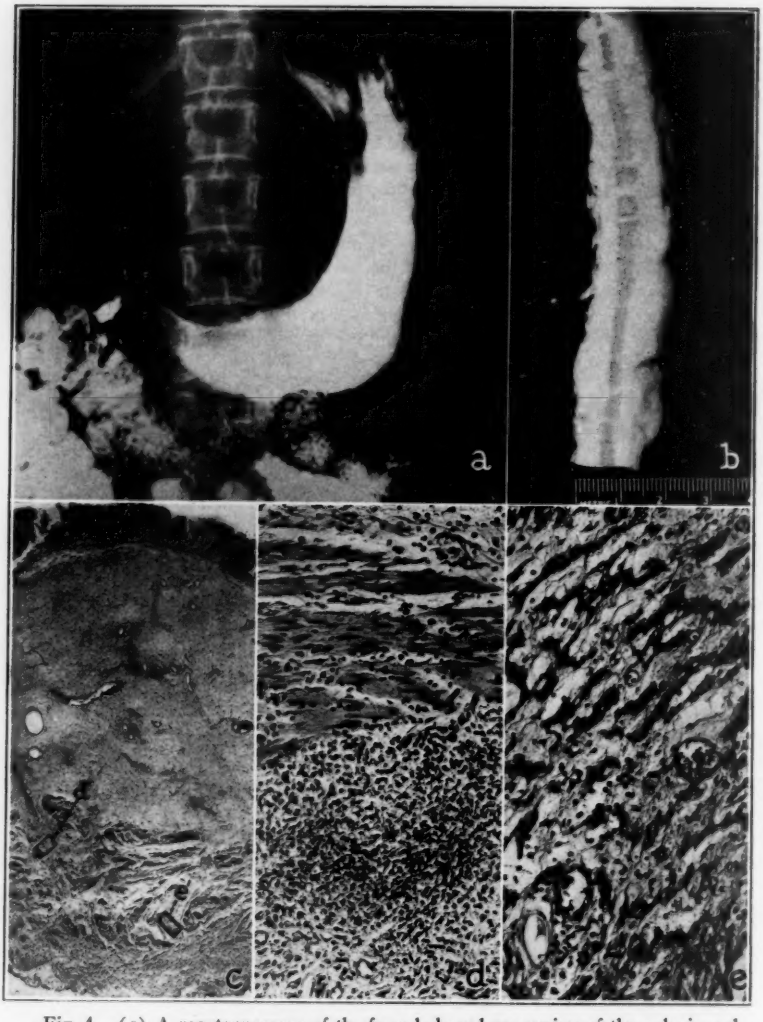


Fig. 4.—(*a*) A roentgenogram of the funnel-shaped narrowing of the pyloric end of the s omach, with absence of peristaltic waves. The rugae in the cardiac portion of the stomach are normal. (*b*) A photograph showing the increased thickness and edema of the wall of the stomach. (*c*) A photomicrograph (× 5.7) demonstrating the increased thickness of the submucosa and the separation of muscle fibers due to edema. The locations of *d* and *e* are indicated at *d'* and *e'*. (*d*) A photomicrograph (× 145) showing infiltration of the muscularis with lymphocytes, large mononuclear cells and polymorphonuclear leukocytes. (*e*) A photomicrograph (× 145) illustrating edema and lymphocytic infiltration of the muscularis.

Roentgen studies (fig. 4*a*) showed the stomach to be elongated and atonic and to contain more fluid than usual. The pyloric end was rigid, funnel shaped and markedly narrowed. In this region peristaltic waves were absent. The corpus and the fundus were normal. There was 30 per cent retention at the end of six hours. On reexamination several days later, after medication with atropine, these findings were unchanged. A diagnosis of infiltrating lesion of the pyloric end of the stomach, probably an annular carcinoma, was made.

At operation the pyloric end of the stomach was found to be markedly thickened, hard and irregular in contour over an area measuring about 8 cm. in diameter. There was no peritoneal involvement. A few small gastric lymph nodes were noted on the side of the lesser curvature. The appearance of the lesion was that of a malignant tumor, and a subtotal gastrectomy was done.

The portion of the stomach removed showed marked changes. The mucosa was dull pale yellow, soft and edematous. The stomach sectioned with increased resistance and had an unusually thick wall, averaging 16 mm. (fig. 4*b*). The submucosa was greatly thickened, pale, glistening and firm. The other coats were moderately thickened and edematous. Microscopically there were diffuse lymphocytic infiltration and edema of all coats. The gastric glands were elongated and tortuous. The submucosa was unusually thick, principally because of edema. There was also edema of the muscularis, with actual separation of the muscle fibers. In all coats there were also focal collections of polymorphonuclear leukocytes, plasma and large mononuclear cells (fig. 4*c*, *d*, *e*). A diagnosis of subacute and chronic gastritis was made.

Case 5.—A 64 year old white woman had had slight indigestion for two years. For five months she had had fairly severe pain in the upper portion of the abdomen, occurring four to five hours after meals, which was relieved by taking food and sodium bicarbonate. She had had persistent abdominal fulness and occasional vomiting. She had not lost any weight. Physical examination revealed nothing abnormal. Laboratory examination of the blood revealed a red cell count of 5,030,000, a hemoglobin concentration of 71 per cent and a white cell count of 10,200. Gastric analysis showed 39 units of free acid and 50 units of total acid. Clinically, carcinoma of the stomach was suspected.

Roentgen examination (fig. 5*a*) revealed a constricting lesion of irregular contour throughout the prepyloric portion of the stomach. The findings were indicative of carcinoma.

Laparotomy revealed a tumor mass in the pyloric region, which was resected.

The wall of the resected portion of the stomach was increased in thickness (averaging 8 mm.) and sectioned with increased resistance. The submucosa was particularly thickened and edematous.

Microscopically there was marked chronic inflammation with diffuse lymphocytic infiltration of all coats. The marked increase in the thickness of the submucosa was due in part to edema and in part to fibrosis (fig. 5*b*, *c*, *d*). In this specimen there was a lesion measuring 7 mm. in diameter which was not identified on gross examination. Microscopically it showed a small area where the mucosa was interrupted. The architectural pattern of the glands was abnormal, and there were unusually large glands, which were lined with atypical epithelium. In some portions the glands were also atypical in shape, and there were groups of epithelial cells without a glandular pattern. These cells were large, variable in size and had bizarre hyperchromatic nuclei. There were no abnormal mitotic figures and no

histologic evidence of invasion of the submucosa. Such lesions have been called carcinoma *in situ* [4] or carcinoma of noninvasive type (fig. 6 *a*, *b*, *c*).

Another finding was the presence of many large atypical cells in the submucosa and the muscularis. These cells were large and varied in size and shape. Many were multipolar and spindle shaped, so that they appeared to be connective tissue cells. They had deeply chromatic nuclei and abundant pinkish blue cytoplasm.

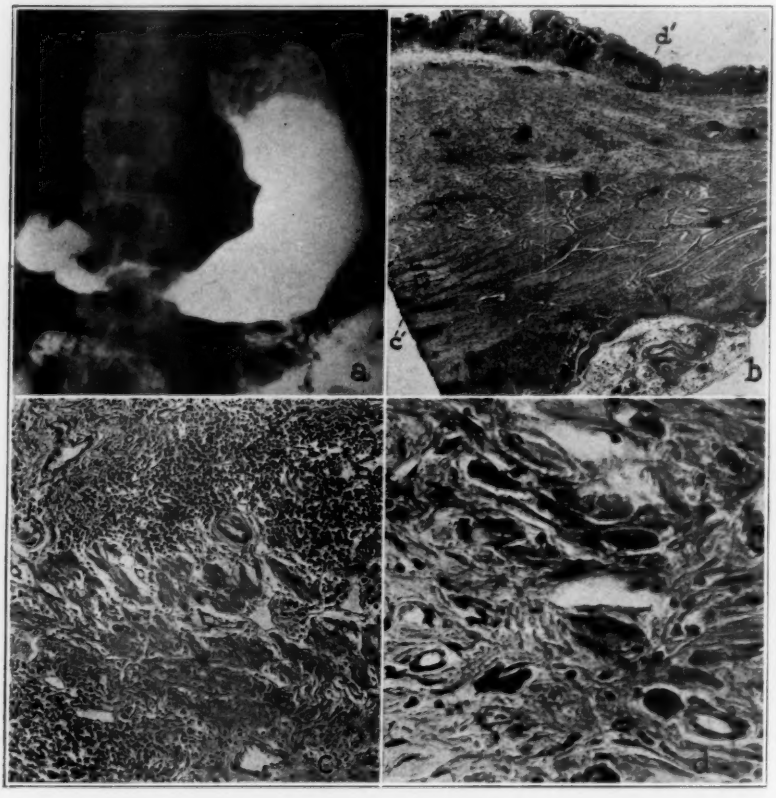


Fig. 5.—(*a*) A roentgenogram demonstrating an irregularly defined constricting lesion in the prepyloric portion of the stomach. (*b*) A photomicrograph (× 6) illustrating lymphocytic infiltration and increased thickness of the wall of the stomach. The locations of *c* and *d* are indicated at *c'* and *d'*. (*c*) A photomicrograph (× 136) showing marked lymphocytic infiltration of the muscularis. (*d*) A photomicrograph (× 332) demonstrating atypical mesenchymal cells in the submucosa.

An occasional cell contained two to four nuclei, but there were no abnormal mitotic figures. Sections stained with mucicarmine showed many of the cells to contain

4. Mallory, T. B.: Carcinoma in Situ of the Stomach and Its Bearing on the Histogenesis of Malignant Ulcers, Arch. Path. **30**:348 (July) 1940.

material that is usually identified as mucin. It is yet to be shown that such a substance is found in or formed by connective tissue cells. It is, therefore, impossible to state that these are not epithelial cells. They have tentatively been considered to be of mesenchymal type. A diagnosis of chronic gastritis and carcinoma *in situ* was made.

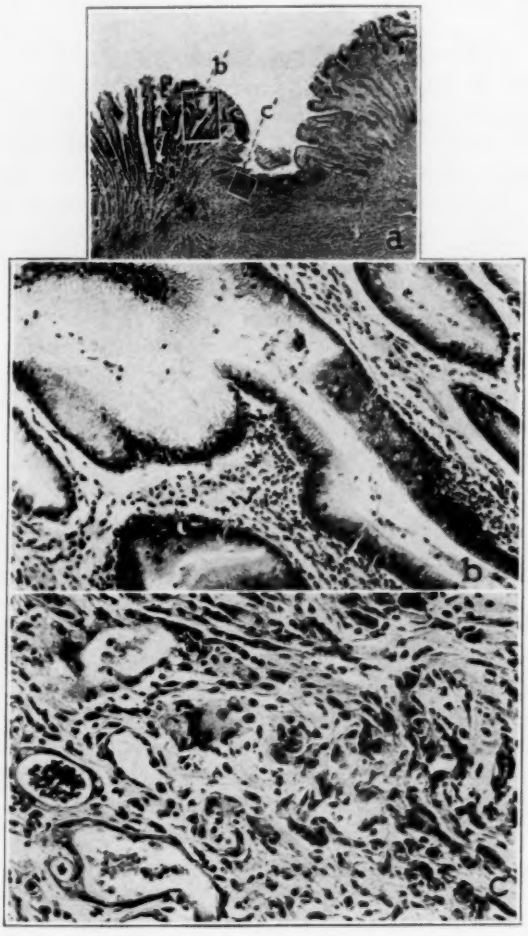


Fig. 6 (*a*) A photomicrograph (× 8) illustrating atypical glands and focal atrophy of the gastric mucosa. The locations of *b* and *c* are indicated at *b'* and *c'*. (*b*) A photomicrograph (× 138) showing giant glands lined with high columnar mucin-secreting epithelium. (*c*) A photomicrograph (× 178) illustrating atypical glands and epithelial cells without a glandular pattern in the gastric mucosa.

This patient is at present, nearly three and one half years after operation, living, well and completely relieved of gastrointestinal symptoms.

COMMENT

From the clinician's standpoint these cases call attention to the difficulties in making a definite diagnosis to guide the management of the patients. Inasmuch as treatment of gastritis is primarily medical unless it produces pyloric obstruction, the importance of utilizing all possible means to establish a diagnosis is obvious.

It is generally admitted that the symptoms of gastritis do not follow any characteristic pattern. In keeping with this opinion the patients in these cases did not have any characteristic complaint except epigastric pain. This, however, varied considerably in degree, duration, radiation, time of occurrence and method of relief. In 4 of the 5 cases the symptoms were associated with considerable loss of weight. The only significant abnormalities noted on physical examination were evidence of loss of weight and anemia. These facts served to enhance the clinical impression of carcinoma.

In regard to laboratory data the gastric analyses did not yield uniform results. Examinations of stools revealed the presence of occult blood in 3 of the 4 cases in which such examination was done. The most uniform finding was a hypochromic anemia, which was fairly severe in some of the cases and undoubtedly resulted from loss of blood. It has been our observation in these and in other cases that the more severe gastritides usually show marked hemorrhagic manifestations on gastroscopic examination. The loss of blood is usually gradual over a long period. It is thus understandable that none of these patients gave any history of melena, although in 1 case occasional vomiting of blood was noted. Attention has, however, been directed in the literature to the fact that gastritis can produce gross and sometimes even fatal hemorrhage. Nevertheless, loss of blood cannot be interpreted as characteristic of chronic gastritis, because carcinoma can produce exactly the same picture.

From the gastroscopic standpoint in the cases in which such examination was done the diagnosis was not definitely made because of the localized, though severe, nature of a lesion which is usually more diffuse and because the adherent secretion masked the true nature of the underlying condition. Since these cases were encountered, the more frequent use of lavage of the stomach preparatory to gastroscopic examination has proved helpful in arriving at a more definite impression in cases in which the diagnosis is questionable.

From the roentgenologist's standpoint the cases reported emphasize the importance of the extreme care necessary before making a diagnosis of carcinoma of the stomach. According to Berg,[5] gastritis is differ-

5. Berg, H. H.: Röntgenuntersuchungen am Innenrelief des Verdauungskanals; Ein Beitrag zur klinischen Röntgendiagnostik insbesondere von Entzündung, Geschwür und Krebs, Leipzig, Georg Thieme, 1930.

entiated from carcinoma either by generalized distribution of widened rugae rearranged in a mosaic-like pattern throughout the entire stomach or by its less frequent localization in the pyloric end. In cases of polypoid gastritis the defects produced may be circular in shape. He also states that chronic gastritis produces intraluminary defects, with occasional roughening and a "toothed contour" of the side of the greater curvature but without marked changes in the contour of the whole stomach. According to Berg, peristaltic waves usually traverse the involved area without interference.

From the reported cases, however, it is apparent that chronic gastritis if localized is not necessarily limited to the pyloric portion of the stomach. Case 1 demonstrates that it may be situated on the side of the greater curvature or, as in cases 3 and 4, it may involve only the cardiac portion of the stomach. Furthermore, chronic gastritis may eventually lead to a rigidity of the wall, with absence of peristaltic waves and to marked deformities of the contour (cases 1, 4 and 5). Occasionally it causes pyloric obstruction (case 4).

If the wide and irregularly arranged linear or polypoid rugae are associated with defects of contour, the differentiation between gastritis and carcinoma may be extremely difficult, indeed impossible. In such instances repeated examinations at short intervals may show some regression in the changes, favoring gastritis. In order to avoid diagnostic errors the roentgenologist must be conscious of these pitfalls and in certain instances should report the possibility of this less serious disease.

The pathologist often sees changes in the gastric mucosa which are slight. In many such instances it may be difficult to decide whether gastritis exists. This difficulty is probably in part due to the fact that the histologic appearance of the normal stomach of the adult is not too well known. It certainly seems possible that a normal adult's stomach is subjected to irritation by ingested coarse, hot and cold food, alcoholic drinks and other irritating substances. It has been shown [6] that although alcohol may produce hyperemia of and petechiae in the gastric mucosa, it does not cause any true inflammation. Berry [7] has pointed out that there is no evidence that significant gastritis results from the ingestion of alcohol provided there is an adequate intake of the vitamin B complex. It seems probable, therefore, that minor changes in the gastric mucosa may result from the ingestion of irritating substances,

6. Hirsch, E. F.: The Gastric Mucosa and Delirium Tremens, Arch. Int. Med. **17**:354 (March) 1916.

7. Berry, L. H.: Chronic Alcoholic Gastritis: Evaluation of the Concept, with Gastroscopic Studies in One Hundred Cases, J. A. M. A. **117**:2233 (Dec. 27) 1941.

but that there is any significant inflammation is questionable. Because such minor changes in the stomach have been interpreted as chronic gastritis, the accuracy of such a diagnosis has frequently been questioned. Changes, however, in the stomach are sometimes encountered which are proof of a disease of unknown causation which is progressive and serious. In such instances the anatomic evidence of inflammation is indisputable. The conditions in all of the cases reported in this paper are of this type and should be considered as chronic nonspecific gastritis.

Chronic gastritis may affect principally the mucosa and the submucosa, or it may involve the entire thickness of the stomach. The types which principally involve the mucosa are usually called either chronic atrophic or chronic hypertrophic gastritis. In none of the cases described was the inflammation limited to the mucosa; in every one there was involvement of all coats of the stomach. The mucosa was in all instances involved and increased rather than decreased in thickness. In most of them varying degrees of acute and subacute inflammation were superimposed on the more marked chronic process. These, therefore, are all cases of chronic interstitial gastritis with hypertrophic mucosa.

The following principal changes were noted:

On gross examination, the stomachs were increased in size and consistency, had unusually thick walls and sectioned with increased resistance. In all, the mucosa was thick, dull and edematous; the submucosa was thick, edematous and in some instances gelatinous, and the muscularis was thick, somewhat edematous and unusually firm. By gross examination alone it was difficult to exclude diffusely infiltrative lesions like those of scirrhous carcinoma, lymphoblastoma and syphilis.

Microscopic examination showed cellular infiltration with lymphocytes, polymorphonuclear leukocytes and plasma cells, of all coats, most marked in the mucosa and the submucosa. There were also edema and fibrosis of all portions, particularly of the submucosa and the muscularis. The gastric glands were somewhat elongated and dilated. In some instances there was metaplasia of the glandular epithelium to the mucin-secreting type.

In case 5, in addition to the gastritis, there was carcinoma limited to the mucosa. Noninvasive epithelial tumors in the uterus [8] and in the stomach [4] are reported in the literature and have been called

8. Schiller, W.: Untersuchungen zur Entstehung der Geschwülste: I. Teil. Collumcarcinom des Uterus, Virchows Arch. f. path. Anat. **263**:279, 1927. Younger, P. A.: Preinvasive Carcinoma of the Cervix, Arch. Path. **27**:804 (April) 1939.

"carcinoma *in situ*." The lesion in this case is that of carcinoma *in situ* with local invasion of the gastric mucosa. Some of the histologic features of this lesion are shown in the photomicrographs. The lesion measures 8 mm. in its greatest diameter, and the mucosa is decreased in thickness in one portion (fig. 6 *a*). In general, there is no striking alteration in the glandular pattern, but there are distinct changes in the size of the glands and in the character of the cells which line them. Some of the glands are unusually large (fig. 6 *b*), and their lining cells have hyperchromatic nuclei and in some instances loss of nuclear polarity. In some regions the glands are atypical in shape, and there are many epithelial cells in the mucosa without a distinct glandular pattern (fig. 6 *c*). Some of these cells are unusually large; most have deeply chromatic nuclei, and a few are multinucleated. At no point in any of the sections is there demonstrable invasion of the submucosa. In this same case atypical cells are scattered throughout the submucosa, the muscularis and the serosa. These cells (fig. 5 *d*) are relatively large and contain material which takes the mucicarmine stain. They have been tentatively identified as mesenchymal in type.

The occurrence of chronic gastritis and gastric carcinoma together suggests a possible relation between the two conditions. At the present time any thought regarding the causation of cancer of the stomach is largely speculative. Many investigators, however, particularly Konjetzny,[2] have expressed the belief that carcinoma never develops in perfectly normal gastric mucosa. They suggested that chronic gastritis is of considerable importance as a basis for carcinoma of the stomach. It is the experience of these investigators that gastric carcinoma is always associated with a pronounced gastritis with either atrophic or atrophic-hypertrophic mucosa.

It must be admitted that "carcinoma *in situ*" is not an outspoken invasive tumor, but it can be considered as a type of preinvasive carcinoma of the stomach. The time at which invasion may begin is, of course, impossible to tell, and it may be a few months or many years. The simultaneous occurrence of chronic gastritis and this noninvasive carcinoma may indicate a relation between the two. There is, of course, a stage in the development of every large carcinoma in which there are only a few malignant cells in the mucosa. Carcinoma *in situ* is thought to be such a lesion. It might thus be the intermediate stage between chronic inflammation of the stomach and outspoken gastric carcinoma.

Chronic gastritis is of utmost importance because of its possible relation to gastric carcinoma.[9] This is readily seen in studies of the

9. Schindler, R.: Early Diagnosis of Cancer of the Stomach: Gastroscopy and Gastric Biopsies, Gastrophotography, and X-Rays, J. Nat. Cancer Inst. **1**:451 (Feb.) 1941. Konjetzny.[2]

statistics of the cure of gastric carcinoma with present methods of diagnosis and therapy. According to Pack and Livingston,[10] three year cures are obtained in 3.2 per cent, five year cures in 1.9 per cent and ten year cures in 0.7 per cent of all cases of gastric carcinoma (both operable and inoperable). In other words, five year cures are obtained in less than 2 of every 100 patients with gastric carcinoma who enter a hospital, in spite of modern surgical treatment. These figures, of course, include many cases of far advanced carcinoma which is inoperable, and certainly when resection of the involved portion of the stomach is feasible, the percentage of five year cures is considerably greater (as high as 20 per cent in some clinics).

One of the reasons for the lack of success in the treatment of this disease is the inability to recognize early stages in spite of the modern methods of diagnosis, which include gastroscopic and roentgen examinations. With present knowledge it must be admitted that a diagnosis of carcinoma *in situ* even with local mucosal invasion can probably never be made by these methods. But there must be even in the most malignant tumors an intermediate stage between the preinvasive or early invasive lesion and the large tumor mass which it would be possible to locate by gastroscopic or roentgen examination. The recognition of such early lesions of minimum size seems at the present time to be the only possible hope for those persons who might eventually be victims of gastric carcinoma.

It is an accepted fact that gastric carcinoma is more likely to develop in patients with chronic gastritis, particularly the atrophic type, than in other healthy adults. It is hoped that the careful follow-up of patients having chronic gastritis, with frequently repeated roentgen and gastroscopic examinations, may lead to the recognition of early carcinomas of minimum size that have not yet invaded lymphatics and have not caused recognizable symptoms. The diagnosis and the surgical treatment of such early carcinomas would in all probability increase the percentage of cures in carcinoma of the stomach.

CONCLUSIONS

Five cases of chronic gastritis simulating carcinoma are reported.

Chronic gastritis in itself may be a serious disease. In some cases it causes pyloric obstruction and may require surgical resection.

The symptoms, signs and roentgen and gastroscopic appearance and even the gross appearance of the stomach are in many instances like those of gastric carcinoma.

---

10. Pack, G. T., and Livingston, E. M.: Treatment of Cancer and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940, vol. 2.

Chronic gastritis may be, at least in some instances, a curable precancerous condition. Carcinoma *in situ* may be considered as a curable preinvasive stage of cancer.

Chronic gastritis is of importance because of its possible relation to gastric carcinoma. Patients with this condition should be carefully followed up with repeated roentgen and gastroscopic examinations to discover, if possible, gastric carcinoma in its early stage and thus increase the percentage of surgical cures of carcinoma of the stomach.

University Hospitals.

INDUCED THIAMINE (VITAMIN B_1) DEFICIENCY IN MAN

RELATION OF DEPLETION OF THIAMINE TO DEVELOPMENT OF BIOCHEMICAL DEFECT AND OF POLYNEUROPATHY

RAY D. WILLIAMS, M.D.
Fellow in Medicine, the Mayo Foundation

HAROLD L. MASON, PH.D.

MARSCHELLE H. POWER, PH.D.
AND
RUSSELL M. WILDER, M.D., PH.D.
ROCHESTER, MINN.

In the first study of isolated thiamine deficiency, which Smith and two of us (R. D. W. and H. L. M.[1]) made in 1939, 4 young women were maintained on a basal diet which provided 0.15 mg. of thiamine per day (0.075 mg. per thousand calories of the diet) for 147 days. Vitamin A, vitamin D, ascorbic acid (vitamin C), niacin (nicotinic acid), riboflavin, iron and calcium were provided as supplements to this diet. The study of severe restriction of thiamine was repeated in 1940 with 4 young women who were maintained on the same basal diet for 88 days.[2] In the later study vitamins of the B complex, other than thiamine, were provided by administration of 20 Gm. of autoclaved brewers' yeast per day. This yeast after autoclaving did not contain any thiamine. Its content of the other factors of the vitamin B complex was less severely affected by autoclaving. Twenty grams of autoclaved yeast contained (by analysis) approximately 1.0 mg. of riboflavin, 0.8 mg. of pyridoxine and 0.6 mg. of pantothenic acid. Two additional subjects, serving as controls, received the same diet supplemented with thiamine hydrochloride, as well as with the autoclaved yeast.

The abnormalities ultimately noted in all the subjects who thus were severely deprived of thiamine for several weeks were depressed mental

From the Division of Biochemistry, Mayo Foundation (Drs. Mason and Power), and the Division of Medicine, Mayo Clinic (Dr. Wilder).

1. Williams, R. D.; Mason, H. L., and Smith, B. F.: Induced Vitamin B_1 Deficiency in Human Subjects, Proc. Staff Meet., Mayo Clin. **14**:787-793 (Dec. 13) 1939.

2. Williams, R. D.; Mason, H. L.; Wilder, R. M., and Smith, B. F.: Observations on Induced Thiamine (Vitamin B_1) Deficiency in Man, Arch. Int. Med. **66**:785-799 (Oct.) 1940.

states, paresthesias, generalized weakness, giddiness, backache, soreness of muscles, palpitation and precordial distress (pseudoangina) on exertion, insomnia, anorexia, nausea, vomiting, loss of weight, atony of muscles, faint heart sounds, lowered blood pressures and bradycardia when the subject was at rest in bed, with tachycardia and sinus arrhythmia on exertion. In all cases, physical activity was greatly decreased and capacity for work fell progressively during the period of restricted intake of thiamine. Electrocardiographic abnormalities developed, and evidence of impairment of gastrointestinal motility was provided by roentgenograms which were taken at intervals after ingestion of a barium sulfate meal. Values for concentration of bisulfite-binding substances, which included pyruvic acid, and for lactic acid in the blood were elevated, irregularly before, but particularly after, exercise and after administration of dextrose. None of these signs and symptoms was observed in the control subjects so long as the intake of thiamine exceeded 0.45 mg. per thousand calories. In general, severe restriction of thiamine was associated ultimately with states of inactivity, apathy, derangement of metabolic processes, loss of weight and prostration.

In a second study[3] the intake of thiamine was restricted less severely. The basal diet, composed of foods commonly appearing on American tables, provided 0.45 mg. of thiamine per day (0.22 mg. per thousand calories). Again, the basal diet was supplemented with minerals, vitamin A, vitamin D, ascorbic acid and autoclaved brewers' yeast and, therefore, it was deficient, so far as could be judged, only in thiamine. The study, beginning July 25, 1940 and ending June 1, 1941, was divided into a foreperiod during which thiamine hydrochloride was administered, a period of restriction of thiamine and an after-period during which thiamine hydrochloride was again administered, the subjects being maintained continuously on the basal diet. Therefore, each subject served as her own control. Eleven subjects were employed in this study. Six of them, after a period of preliminary restriction of thiamine, received thiamine hydrochloride in increasing amounts for the purpose of study of thiamine requirements. This group of 6 subjects served in some degree as controls for the group of 5 subjects who were deprived of thiamine for periods as long as 196 days. In this study moderate, prolonged restriction of thiamine, but not of calories, was associated with states of emotional instability, reflected by irritability, moodiness, quarrelsomeness, lack of cooperation, vague fears progressing to agitation, mental depression, variable restriction of activity and numerous somatic complaints. Detectable metabolic disturbances, occurring irregularly, were of variable degree of severity and were reflected in disturbance of function of various

3. Williams, R. D.; Mason, H. L.; Smith, B. F., and Wilder, R. M.: Induced Thiamine (Vitamin B_1) Deficiency and the Thiamine Requirement of Man: Further Observations, Arch. Int. Med. **39**:721-738 (May) 1942.

tissues of the body. None of these signs, symptoms or metabolic defects were observed in the control subjects when their intakes of thiamine exceeded 0.5 mg. per thousand calories.

Neither acute, severe deprivation nor moderate, prolonged deprivation of thiamine produced the classic syndrome of beriberi which has been observed in the Orient. In severe restriction of thiamine prostration and inanition precluded continuation of deprivation just when neuropathy appeared certain of development. In prolonged moderate restriction of thiamine general impairment of mental and physical health was the predominant manifestation of deficiency disease. Therefore, it appeared likely that restriction of thiamine to a degree intermediate between 0.075 and 0.22 mg. per thousand calories might induce, within a reasonable period, the syndrome of beriberi. The recent studies of Swank and Bessey [4] of avian thiamine deficiency indicated that less severe restriction of thiamine or periodic administration of small doses of thiamine enabled pigeons to live until polyneuropathy developed. Likewise, we believed that the procedure of "partial periodic cure" would serve to maintain a more satisfactory level of activity and to restore the flagging appetite of the subject. Therefore, in a third study, reported here, a diet was constructed so that it provided 0.1 mg. of thiamine per thousand calories, which would be increased to approximately 0.175 mg. per thousand calories by periodic administration of small doses of thiamine hydrochloride. Adoption of this method of study also enabled us to determine periodically the excretion of a test dose of thiamine, which was a second purpose of the study.

Our earlier studies clearly indicated that the ordinary excretion of thiamine for twenty-four hours reflected closely the current intake of thiamine. They also showed that excretion after subcutaneous administration of a test dose of 1.0 mg. of thiamine hydrochloride reflected closely the "apparent" stores of thiamine in the tissues. Two of us (H. L. M. and R. D. W.) have discussed the significance of tests of excretion in another paper.[5]

Since 1939 we have accumulated data on the content of pyruvic acid, lactic acid, bisulfite-binding substances and dextrose in the blood after exercise and after administration of various carbohydrates, such as dextrose, lactate, pyruvate, levulose and sucrose, in normal and in thiamine-deficient subjects. Details of the accumulated data will be presented later. Suffice it to state here that determinations of pyruvic acid, lactic acid and dextrose in the blood after oral or intravenous administra-

4. Swank, R. L., and Bessey, O. A.: Avian Thiamine Deficiency: Characteristic Symptoms and Their Pathogenesis, J. Nutrition **22**:77-89 (July) 1941.

5. Mason, H. L., and Williams, R. D.: The Urinary Excretion of Thiamine as an Index of the Nutritional Level: Assessment of the Value of a Test Dose, J. Clin. Investigation **21**:247-255 (March) 1942.

tion of dextrose appear to be the most reliable and generally applicable of the several test procedures which we have used for estimation of probable severity of the metabolic defect in states of thiamine deficiency, uncomplicated by other states of disease. The data indicate that in states of thiamine deficiency the values for pyruvic acid and lactic acid in the blood are abnormally elevated, infrequently when the subject is in the basal postabsorptive state or at rest in bed, but regularly after administration of dextrose.

We have selected the following procedures for the tests, which are performed with the subject in the basal state: For the intravenous test 0.4 Gm. of dextrose (0.8 cc. of 50 per cent solution of dextrose) per kilogram of body weight is injected intravenously in three minutes. Samples of blood for analysis of content of pyruvic acid,[6] lactic acid [7] and dextrose are taken just before injection and at thirty, sixty and one hundred and twenty minutes after injection. The value for pyruvic acid and for lactic acid at thirty minutes is most significant. This intravenous test is made when nausea prevents administration by mouth. Otherwise an oral test is used. For the oral test, 50 Gm. of dextrose in 250 cc. of solution is administered and thirty minutes later another 50 Gm. of dextrose is given, as in a dextrose tolerance test as performed by Exton and Rose.[8] Samples of blood for analysis are taken just before administration of the first dose of dextrose and at thirty, sixty and ninety minutes after administration of the first dose. The values for pyruvic acid, lactic acid and dextrose obtained at sixty and ninety minutes are most significant. An earlier detection of the state of thiamine deficiency is possible with this larger "metabolic load" test of 100 Gm. of dextrose. Division of the total dose of dextrose has reduced the incidence of emesis, a frequent complication of the test in thiamine deficiency. In general, the higher values for pyruvic acid have been encountered in the more severe states of thiamine deficiency. The general nature of the accumulated data of the dextrose tolerance tests is indicated in figures 1 and 2 and in table 1.

The "metabolic load" test is not a specific test for thiamine deficiency, and unless it is performed with the subject in the basal state, results of the test cannot be interpreted with any degree of precision. For example, we found that administration of dextrose to a person suffering from "total" diabetes was not associated with a rise of pyruvic acid in the blood

6. Beuding, E., and Wortis, H.: The Stabilization and Determination of Pyruvic Acid in the Blood, J. Biol. Chem. **133**:585-591 (April) 1940.

7. Barker, S. B., and Summerson, W. H.: The Colorimetric Determination of Lactic Acid in Biological Materials, J. Biol. Chem. **138**:535-554 (April) 1941.

8. Exton, W. G., and Rose, A. R.: Diabetes as a Life Insurance Selection Problem, Proc. A. Life Insur. M. Dir. America (1931) **18**:252-273. Matthews, M. W.; Magath, T. B., and Berkson, J.: The One Hour-Two Dose Dextrose Tolerance Test (Exton-Rose Procedure): Diagnostic Significance, J. A. M. A. **113**:1531-1537 (Oct. 21) 1939.

unless insulin had been administered previously. Administration of dextrose to a subject who had "alimentary glycosuria" was associated with abnormally high values for pyruvic acid. Administration of dextrose to subjects who had states of hypermetabolism, induced by administration of desiccated thyroid, was associated with abnormal elevations of pyruvic acid in the blood. Presumably in the case of diabetes mellitus either the rates of removal of pyruvic acid and lactic acid were increased or their rates of formation considerably decreased at the blood sugar levels studied (200 to 600 mg. per hundred cubic centimeters of blood). In the cases of induced hypermetabolism the values for dextrose in the blood did not reach abnormal heights, and therefore, the high values for pyruvic acid were caused by either unusual rapidity of mobilization of

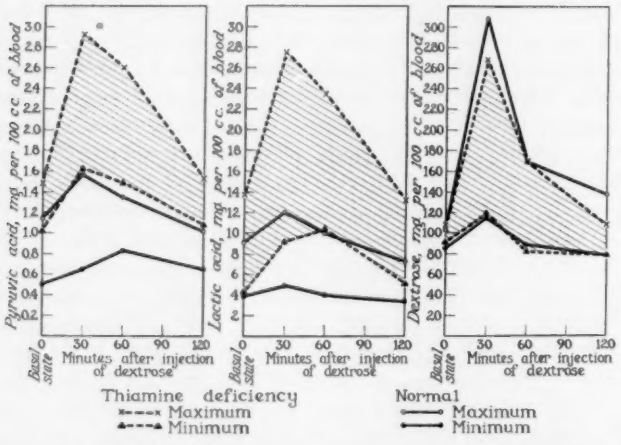


Fig. 1.—The range of values for pyruvic acid, lactic acid and dextrose in the blood after intravenous administration of dextrose (0.4 Gm. of dextrose per kilogram of body weight in three minutes). Data for "normal" were obtained in studies on 12 physically normal subjects who were known to have been well supplied with thiamine and otherwise received the same nutrients as the thiamine-deficient subjects. Data for "thiamine deficiency" were obtained in studies on 7 subjects who had been maintained for periods of various duration on standard diets which provided either 0.1 or 0.2 mg. of thiamine per thousand calories and who, therefore, were known to be in states of thiamine deficiency.

intermediary metabolites or abnormally slow rates of utilization of the metabolites.

METHODS

The subjects for this, as for our previous investigations of thiamine restriction, were chosen from among inmates of a large hospital for psychopathic persons. They had "recovered" from acute phases of mental illness and were able to exercise an informed decision in volunteering for this service. The consent of nearest of kin and of guardians was also obtained. In the present study a group of several

women received an ample diet for a period of 52 days, whereby a good nutritional status could be assured. During this time they became familiar with ward routines and analytic procedures and were observed closely. After this period of preliminary observation 2 of the group were selected for the study reported here. The final selection was made on the basis of willingness and ability to cooperate, absence of evidence of abnormal nutrition and absence of significant physical or emotional abnormality. The subjects, under close observation, continued to be engaged in activities of the ward, such as housekeeping and laundering.

The basal diet was arranged to provide not more than 0.1 mg. of thiamine for each 1,000 calories. The variety of foods necessarily was limited. They were white flour, sugar, tapioca, corn starch, polished rice, raisins, egg white, cottage cheese, American cream cheese, butter, hydrogenated fat, tea and cocoa. Samples

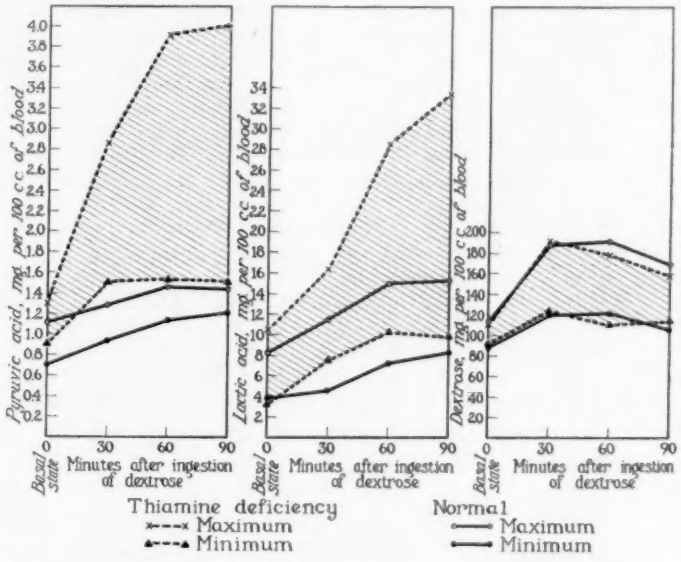


Fig. 2.—The range of values for pyruvic acid, lactic acid and dextrose in the blood after oral administration of dextrose (50 Gm. dextrose in 250 cc. of solution at zero time and 50 Gm. at thirty minutes). Data for "normal" were obtained in studies on 11 physically normal subjects who were known to have been well supplied with thiamine and otherwise received the same nutrients as the thiamine-deficient subjects. Data for "thiamine deficiency" were obtained in studies on 10 subjects who had been maintained for periods of various duration on standard diets which provided either 0.1 or 0.2 mg. of thiamine per thousand calories. Thus, these subjects were known to be in states of thiamine deficiency.

of the individual foods, as well as samples of the composite diet, were analyzed for their content of thiamine. The analysis for thiamine was made by the method of Hennessy.[9] The basal diet contained approximately 250 Gm. of carbohydrate,

9. Hennessy, D. J.: Chemical Methods for the Determination of Vitamin B_1. Indust. & Engin. Chem. (Analyt. Ed.) **13**:216-218 (April 15) 1941.

TABLE 1.—*Concentration of Pyruvic Acid, Lactic Acid and Dextrose in the Blood After Intravenous Administration of Dextrose at Intervals During Development of Thiamine Deficiency*

Period of Restriction of Thiamine, Days	Urinary Excretion of Thiamine in 24 Hours, Micrograms	Urinary Excretion of Test Dose of 1 Mg. of Thiamine Hydrochloride in 4 Hours, Micrograms	Clinical Estimate of Degree of Deficiency State *	Concentration at Given Intervals After Administration of Dextrose, Mg. per 100 Cc. of Blood											
				Pyruvic Acid				Lactic Acid				Dextrose			
				Basal State	30 Minutes	60 Minutes	120 Minutes	Basal State	30 Minutes	60 Minutes	120 Minutes	Basal State	30 Minutes	60 Minutes	120 Minutes
Subject 1: A Woman Aged 36, 168 Cm. Tall, Weighing 56.5 Kg.															
0	480	538	0	0.7	0.9	1.1	0.7	6.3	11.9	7.6	4.8	92	116	86	91
33	10	113	1	0.8	1.4	1.2	0.8	6.5	14.9	8.6	5.8	98	125	98	105
65	6	64	2	1.2	1.8	1.6	1.1	9.2	18.7	12.6	8.2	101	118	84	86
83	14	13	3	0.9	2.2	1.8	1.0	7.5	15.4	16.6	6.8	99	128	105	92
116	8	39	4	1.5	3.2	2.6	1.5	8.1	15.6	21.2	11.7	...	...	...	...
Subject 2: A Woman Aged 48, 161 Cm. Tall, Weighing 55 Kg.															
0	450	548	0	0.8	1.3	1.2	0.7	3.8	7.9	6.5	3.5	91	155	100	78
35	10	96	1	1.0	1.5	1.2	1.0	6.5	9.6	8.1	6.7	100	163	98	80
63	12	74	2	1.2	2.3	1.9	0.9	7.3	19.6	16.1	5.6	97	158	96	86
83	11	58	3	1.0	2.0	2.2	1.0	6.2	16.6	15.3	7.2	102	165	138	96
110	6	37	4	1.2	2.3	2.1	1.1	5.4	17.0	14.6	6.0	105	178	125	96

* 1, minimal state of thiamine deficiency; 2, moderately advanced state; 3, far advanced state, and 4, anatomic defect.

60 Gm. of protein and 90 Gm. of fat. The caloric intake was adjusted to the requirement of each subject by giving fractions or multiples of the standard diet. By this procedure the ratio of thiamine to calories was maintained nearly constant. The diet was supplemented with 0.2 Gm. of halibut liver oil fortified with irradiated ergosterol (0.2 Gm. of which provided 10,000 international units of vitamin A and 4,000 international units of vitamin D), 120 mg. of ascorbic acid, 1.0 mg. of riboflavin, 2.0 mg. of pyridoxine, 5.0 mg. of calcium pantothenate, 20.0 mg. of nicotinic acid amide, 0.25 Gm. of choline chloride, 0.2 Gm. of inositol, 0.2 Gm. of ferrous sulfate and 0.6 Gm. of tricalcium phosphate.[10] Iodized table salt (sodium chloride) was used in the preparation of the diet.

Excretion of thiamine for twenty-four hours was determined once each week, and excretion of the test dose of 1.0 mg. of thiamine hydrochloride administered subcutaneously was determined approximately every two weeks. The test dose was administered to the subject in the postabsorptive state, and urine was collected for four hours after the injection. As has been stated, this periodic administration of the test dose raised the average intake of thiamine to approximately 0.175 mg. per thousand calories. Content of pyruvic acid, lactic acid and dextrose in the blood after intravenous administration of dextrose, as previously described; body weight; physical and neurologic signs; electrocardiographic changes; motility of the gastrointestinal tract as estimated by roentgen examination; blood counts; serum protein and basal metabolic rates had been determined during the period of preliminary observation. They were determined at intervals during the period of deprivation of thiamine and again during the period in which the basal diet, deficient in thiamine, was supplemented with thiamine hydrochloride. Needless to say, the carrying out of observations of this nature entailed unusual cooperation of nursing and dietary assistants. This work was made possible by the assistance of Miss Margaret Pewters, Miss Phyllis Newman, Mrs. H. H. Pattinson, Miss Fern Dahlgren and Miss Jane Spence.

OBSERVATIONS ON SUBJECTS WHILE THEY WERE RECEIVING THE DIET DEFICIENT IN THIAMINE

The period of restriction of thiamine began Sept. 23, 1941 and ended Jan. 20, 1942 (120 days). Deprivation of thiamine was discontinued because in case 1 a severe neurologic defect had developed and in case 2 less severe, but nevertheless definite, signs of neurologic defects had appeared. The appetites of both subjects had failed, and inanition seemed imminent.

The intake and excretion of thiamine, the intake of food and data on values for pyruvic acid after intravenous administration of dextrose are presented in figures 3 and 4. Data on excretion of thiamine after injection of a test dose of thiamine hydrochloride (an index of the depletion of tissue stores of thiamine), values for pyruvic acid and lactic acid after administration of dextrose (a suggestive index of severity of biochemical defect), the activity of the patellar and the achilles tendon reflexes and ability of the subject to rise from the squatting position (suggestive indexes of neurologic damage) are summarized in tables

10. Dr. D. F. Robertson, Associate Medical Director, Merck and Company, Inc., Rahway, N. J., supplied us with thiamine hydrochloride, riboflavin, pyridoxine, calcium pentothenate and choline chloride.

2 and 3. The clinical courses of the 2 subjects during the development of thiamine deficiency are presented in greater detail later in the reports of progress of subjects. Details of the responses of the patients to treatment with thiamine hydrochloride will be presented in another article. It suffices to state here that administration of 60 to 80 mg. of thiamine hydrochloride both orally and parenterally corrected, in part, the gross biochemical defect within a week. Appetite, strength (in the absence of paralysis) and feeling tone had improved greatly by the seventh day and had returned to the norm for the subject within thirty days. However, the more severe neurologic defects in case 1 were not fully corrected by inten-

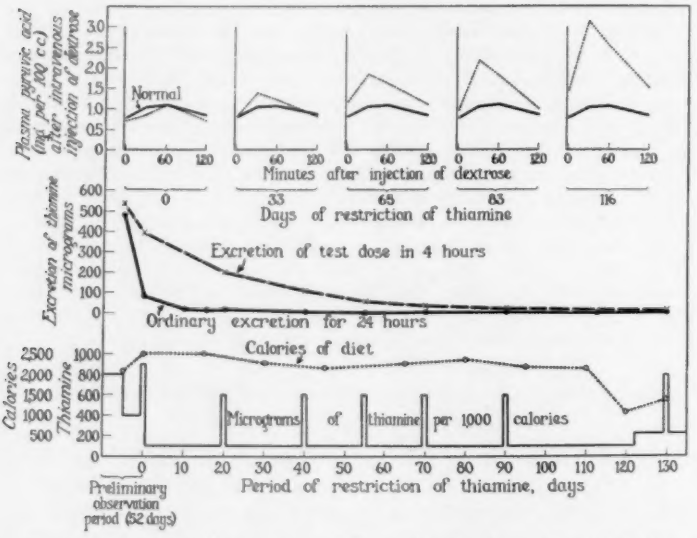

Plasma pyruvic acid (mg. per 100 cc.) after intravenous injection of dextrose
Normal
Minutes after injection of dextrose
Days of restriction of thiamine
Excretion of thiamine micrograms
Excretion of test dose in 4 hours
Ordinary excretion for 24 hours
Calories of diet
Calories
Thiamine
Micrograms of thiamine per 1000 calories
Preliminary observation period (52 days)
Period of restriction of thiamine, days

Fig. 3 (case 1).—Intake and excretion of thiamine; excretion of a test dose of thiamine (1.0 mg. thiamine hydrochloride was injected subcutaneously; the excretion in four hours after injection was determined; the subject was fasting), and data on pyruvic acid in the whole blood (not plasma as indicated in the figure) after intravenous administration of dextrose. The data for the top row of figures are taken from table 1.

sive treatment with thiamine hydrochloride for 120 days, although movements of extension, flexion, abduction and adduction of the thighs and legs had become progressively stronger. The achilles tendon and the patellar reflexes in case 1 remained absent after 121 days of treatment. The less advanced neurologic defects in case 2 were corrected by intensive treatment (15 mg. of thiamine hydrochloride per day) for 60 days.[10a]

10a. The subject of case 1 was reported Dec. 15, 1942 to have recovered normal strength in the muscles previously affected.

REPORTS OF PROGRESS OF SUBJECTS

CASE 1.—The subject was an active, vigorous and industrious woman aged 36, 168 cm. tall and weighing 56.5 Kg. She had been engaged for several months in laundering. Her cooperation in the matter of eating and, so far as her strength would permit, in working was entirely satisfactory. The clinical course of this subject was not complicated by intercurrent infections. Body temperatures were not observed to be abnormal at any time.

Observations at 30 Days.—Anorexia had developed. The subject was weak and thereafter voluntarily restricted the duration and vigor of her activities.

Observations at 50 Days.—The subject complained of nausea and epigastric distress and vomited occasionally after meals. The values for pyruvic acid in the blood after administration of dextrose were abnormally high.

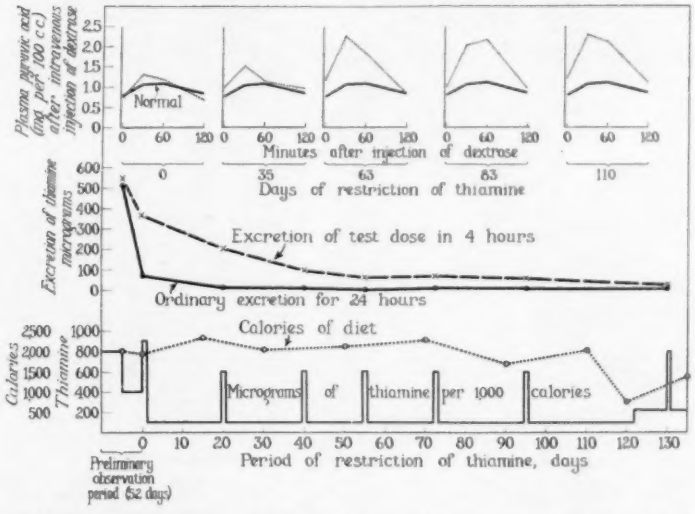

Plasma pyruvic acid (mg. per 100 c.c.) after intravenous injection of dextrose
Normal
Minutes after injection of dextrose
Days of restriction of thiamine
Excretion of thiamine micrograms
Excretion of test dose in 4 hours
Ordinary excretion for 24 hours
Calories of diet
Calories
Thiamine
Micrograms of thiamine per 1000 calories
Preliminary observation period (52 days)
Period of restriction of thiamine, days

Fig. 4 (case 2).—Intake and excretion of thiamine; excretion of a test dose of thiamine (1.0 mg. of thiamine hydrochloride was injected subcutaneously; the excretion in four hours after injection was determined; the subject was fasting), and data on pyruvic acid in the whole blood (not plasma as indicated in the figure) after intravenous administration of dextrose. The data for the top row of figures are taken from table 1.

Observations at 70 Days.—Nausea was constantly present; weakness was severe. The subject limited her activities to assisting with the lighter duties of the ward and frequently did not complete the tasks. She was apathetic and confused and at times made complaints of numbness and tingling (paresthesia) of the medial surfaces of the legs from the knees to the ankles.

Observations at 90 Days.—Spontaneous exertions had almost ceased; interest in reading was conspicuously absent. Interpretation of the stimulus of a wisp of cotton and of a pinprick applied to areas on the medial surfaces of the legs was inaccurate. Muscles of the calves of the legs were tender and ability to rise

from the squatting position was definitely impaired. The patellar reflexes were slightly hyperactive; the achilles tendon reflexes were hypoactive.

Observations at 110 Days.—The appetite had failed; apathy, vagueness and confusion were conspicuous. The blood pressure was 100 mm. of mercury systolic and 65 mm. diastolic; the cardiac rate was variable but usually slow (55 to 65 beats per minute) during rest in bed and rapid (90 to 120 beats per minute) on ordinary exertions. The heart sounds were faint. Application of a wisp of cotton

TABLE 2.—*Development of Biochemical Defect of Thiamine Deficiency in Subject 1* *

Day of Period	Excretion of Thiamine in 24 Hr., Micrograms	Excretion of Test Dose of 1 Mg. of Thiamine Hydrochloride in 4 Hr., Micrograms	Thirty Minutes After Administration of Dextrose, Mg. per 100 Cc.		Patellar Tendon Reflex†	Achilles Tendon Reflex†	Ability to Rise from Squatting Position†	Symptoms or Signs Which Were Persistent
			Pyruvic Acid	Lactic Acid				
Period of Preliminary Observation								
52	480	538	0.86	11.9	0	0	0	None
Period of Restriction of Thiamine								
10	19	200	....	....	0	0	0	None
30	10	113	1.36	14.9	0	0	0	Anorexia, weakness
50	6	64	....	....	0	0	—1	Nausea, weakness, epigastric pain
70	11	101	1.84	18.7	0	0	—1	Nausea, weakness, sensation of numbness below knees
90	14	12	2.18	15.4	+2	—1	—2	Weakness, giddiness, occasional emesis, sensation of numbness below knees
110	10	20	....	....	—3	—4	—3	Frequent emesis, extreme weakness, apathy, frequent stumbling, sense of touch and vibration impaired below knees
120	8	39	3.19	15.6	—4	—4	—4	Loss of weight, mental confusion, prostration, sense of touch and vibration impaired at knees and ankles, paralysis of quadriceps femoris
Period of Intensive Treatment with Thiamine Hydrochloride ‡								
10	..	..	1.48	11.0	—4	—4	—4	Return of appetite, no further loss of weight, less mental confusion, paralysis of quadriceps femoris
30	..	..	1.35	13.0	—4	—4	—4	Good appetite, gain in weight, less mental confusion, return of interest, paralysis persistent

* A woman aged 36, 168 cm. tall, weighing 56.5 Kg.
† 0, normal, and —4, absent.
‡ More than 60 mg. of thiamine hydrochloride per day.

and pinprick to the medial surfaces of the legs evoked delayed and inaccurate responses. The vibratory sense at the knees and ankles was impaired but not absent. Although a defect of the sense of active or passive position of the knee and ankle joints could not be demonstrated with any degree of certainty, the subject walked with little flexion of the knees and frequently stumbled. She could rise from the squatting position only with some assistance but could stand on her heels and toes and on one foot. Up to the one hundred and tenth day there had been a slight gain of weight (3.8 Kg.), but during the ensuing 10 days a loss of weight (2.7 Kg.) occurred.

Observations at 120 Days.—The data of several examiners[11] indicated that acuity of perception of touch, pain and two points was impaired, with response delayed, over the medial surface of the thighs and especially the legs, but that appreciation of differences of temperature was not impaired over the same area or elsewhere. Sense of vibration was impaired at the ankles but not at the knees. Sense of position of the joints of the toes and legs was not impaired. Movements of abduction, adduction and flexion of the thighs and legs were weak. Extension of the legs, involving chiefly the quadriceps femoris muscles, was barely perceptible. The subject could neither stand nor walk without support. The patellar and the achilles tendon reflexes were absent; clonus could not be elicited at the knees or ankles; a Babinski reflex was not elicited.

TABLE 3.—*Development of Biochemical Defect of Thiamine Deficiency in Subject 2* *

Day of Period	Excretion of Thiamine in 24 Hr., Micrograms	Excretion of Test Dose of 1 Mg. of Thiamine Hydrochloride in 4 Hr., Micrograms	Thirty Minutes After Administration of Dextrose, Mg. per 100 Cc.		Patellar Tendon Reflex†	Achilles Tendon Reflex†	Ability to Rise from Squatting Position†	Symptoms or Signs Which Were Persistent
			Pyruvic Acid	Lactic Acid				
			Period of Preliminary Observation					
52	450	548	1.36	7.9	0	0	0	None
			Period of Restriction of Thiamine					
10	15	194	....	....	0	0	0	None
30	10	96	1.50	9.6	0	0	0	Anorexia, weakness
50	5	73	....	....	0	0	—1	Nausea, epigastric pain, constipation, weakness
70	12	74	2.26	19.6	0	0	—2	Nausea, weakness, apathy, inactivity
90	11	58	2.00	16.6	+2	+1	—2	Nausea, occasional emesis, inactivity, mental confusion
110	8	..	2.27	17.0	—1	—2	—3	Aversion to food, giddiness, weakness, inactivity, prostration, slight impairment of sense of touch and vibration
120	3	37	2.64	17.2	—3	—3	—3	Frequent emesis, loss of weight, prostration, slight impairment of sense of touch and vibration at knee annd ankle
			Period of Intensive Treatment with Thiamine Hydrochloride‡					
10	..	..	1.61	8.5	—2	—3	—2	Improved appetite, no further loss of weight, increased strength, greater activity
30	..	..	1.18	7.8	0	0	0	Good appetite, gain of weight, return of interest, participation in housework

* A woman aged 48, 161 cm. tall, weighing 55 Kg.
† 0, normal, and —4, absent.
‡ More than 15 mg. of thiamine hydrochloride per day.

The initial pressure of the cerebrospinal fluid was 80 mm. of water. The pressure rose promptly when the jugular veins were compressed and fell promptly when pressure on the veins was relaxed. The Kolmer and the Kline reaction of the fluid was negative; the Nonne-Apelt reaction was negative; the colloidal gold (Lange) reaction was interpreted as 000 000 000 0, and there was 1 small lymphocyte per cubic millimeter of fluid. There were, per hundred cubic centi-

11. Dr. H. W. Woltman and Dr. J. R. Campbell made a neurologic examination at this date.

meters of fluid, 20 mg. of protein, 63 mg. of sugar, 710 mg. of chloride and 1.26 mg. of pyruvic acid.

CASE 2.—The subject was an inactive woman aged 48, 161 cm. tall and weighing 55 Kg. In contrast to the subject in case 1 she was neither vigorous nor industrious. Although sedentary in her habits, she assisted with the lighter tasks of housework. Her cooperation in eating and in working, after the first few weeks of deprivation, was poor. Weakness and anorexia were experienced at about the thirtieth day, and thereafter it required considerable persuasion to maintain caloric intake and activity at satisfactory levels.

Observations at 50 Days.—The concentration of pyruvic acid in the blood after injection of dextrose was abnormally high. Complaints of anorexia were continuous; emesis was observed occasionally.

Observations at 70 Days.—The values for pyruvic acid after injection of dextrose had become considerably higher, and emesis after meals had become a more frequent occurrence. Complaints were of nausea, epigastric pain, constipation, weakness and giddiness.

Observations at 90 Days.—Apathy, mental confusion and inactivity had become more conspicuous. There was some tenderness of the muscles of the calves, but the subject could rise from the squatting position without assistance.

Observations at 110 Days.—Severe nausea with frequent emesis after meals associated with epigastric pain and a high degree of generalized muscular weakness was observed. The blood pressure was 95 to 105 mm. of mercury systolic and 60 to 72 mm. diastolic. The cardiac rate at times of rest in bed was slow (50 to 70 beats per minute), changing after moderate exertion to 100 to 120 beats per minute. Complaints were made of numbness and tingling of the anteromedial surfaces of the thighs and legs. Interpretations of stimuli, such as a wisp of cotton, pinprick and warm and cool tubes, were essentially accurate, although responses to stimuli were delayed considerably. Impairment of the sense of vibration and of the sense of position could not be demonstrated. The subject could stand on her heels and toes and on one foot, but rising from the squatting position was accomplished only with some assistance. The achilles tendon and the patellar reflexes were somewhat hyperactive but clonus could not be elicited at the ankle or knee. A Babinski sign was not elicited.

Deprivation of thiamine up to the one hundred and tenth day had been associated with a slight gain of weight (2.3 Kg.), but in the ensuing 10 days, the appetite failed and there was a loss of 2.7 Kg. There was a rapid progression of the apathy and weakness. Emesis became frequent and severe.

Observations at 120 Days.—The blood pressure was 90 to 98 mm. of mercury systolic and 50 to 60 mm. diastolic; the cardiac rate at rest in bed was slow (58 to 68 beats per minute); there was marked sinus arrhythmia, and pallor and giddiness were observed with changes from the recumbent to the erect position. The subject walked with little flexion of her knees and occasionally stumbled. Inattention on her part made for difficulty in interpretation of the data of the sensory examination. The responses to the stimulus of a wisp of cotton and of a pinprick, applied below the knees, were always delayed, uncertain and frequently inaccurate. A defect of the sense of position of the legs and toes could not be elicited; the sense of vibration was impaired but not absent at the ankles. Standing on heels and toes and on one foot was done with much swaying. Rising from the squatting position could be accomplished only with assistance. The patellar tendon reflexes were hypoactive but could be obtained with Jendrassik

reenforcement; the achilles tendon reflexes were absent. A Babinski reflex was not to be elicited.

The pressure of the cerebrospinal fluid was 140 mm. of water. The pressure rose promptly when the jugular veins were compressed and fell promptly when the pressure on the veins was relaxed. The Kolmer and the Kline reaction was negative; the Nonne-Apelt reaction was negative, and the colloidal gold (Lange) reaction was read 011 100 000 0. The cerebrospinal fluid contained, per hundred cubic centimeters, 35 mg. of protein, 56 mg. of sugar, 749 mg. of chlorides and 1.25 mg. of pyruvic acid.

COMMENT

Evidence of deprivation of thiamine was first manifested in these 2 subjects by low levels of thiamine excreted in the urine. Evidence of some degree of deficiency of thiamine was first manifested by lower levels of excretion after administration of a test dose of thiamine hydrochloride. Almost simultaneously with significant decrease of excretion of the test dose of thiamine the values for pyruvic acid in the blood after administration of dextrose became elevated, and the subjects became listless and complained of anorexia and fatigue. Listlessness progressed to apathy, anorexia progressed to nausea and fatigue progressed to prostration, almost stepwise with the decrease of excretion of the test dose of thiamine and with elevation of the level of pyruvic acid in the blood. Symptoms suggestive of dysfunction of the central and the peripheral nervous pathways preceded by months the gross signs of neurologic dysfunction. However, after 110 days defects of the cutaneous sensory pathways, depression or disappearance of the tendon reflexes and paralysis of the muscles of the thighs and legs became apparent.

In our earlier studies of severe restriction of thiamine evidence of polyneuropathy, as manifested by loss of patellar and achilles tendon reflexes and paralysis of the quadriceps femoris muscles, was observed in only 1 of 8 subjects. At that time, mainly because the abnormality was mild, its significance in the light of the studies reported here was not appreciated. In a second study [3] of prolonged, moderate restriction of thiamine some degree of weakness of muscles and paresthesias of the medial surfaces of the legs were observed in subjects who were deprived of thiamine for periods of 88 to 196 days, but paralysis of muscles and loss of tendon reflexes were not observed. Reconsideration of the data of these earlier studies suggests that in the first study the restriction of thiamine was too severe for maintenance of the organism, and therefore, deprivation had to be discontinued before much neuropathy could develop, and that in the second study the restriction was not severe enough for production of objective neurologic defects within the periods of observation.

In the study here reported the dietary restriction of thiamine was intermediate, and administration at periodic intervals of approximately

two weeks of a test dose of 1.0 mg. of thiamine hydrochloride exerted a temporary recuperative effect. Invariably appetite would be improved and activity would be resumed for 7 to 10 days after injection of the test dose.

Studies by Leblond and Chaulin-Serviniere,[12] reported since our observations were made, provide data which are consistent with our experience in human subjects. Using monkeys, the authors found that when the intake of thiamine was low, death would occur before any outstanding clinical symptoms of beriberi developed, whereas when the intake represented about half the minimal requirement of thiamine, clinical signs of polyneuritis, cardiac failure and at autopsy peripheral nerve degeneration were obtained.

We realize that the neuropathy which developed in our subjects might have been caused by factors which were unrelated to deprivation of thiamine. We are aware of the general belief that there are many and exceedingly obscure causes of neuropathy. However, that deficiency of thiamine was the most probable ultimate cause of the polyneuropathy in our subjects is indicated by the following considerations:

1. The neuropathy developed progressively in the period of isolated deprivation of thiamine and regressed when thiamine hydrochloride was provided again and no other changes were made in the regimen.

2. Twenty subjects, including the subjects of the present study, were maintained in the same isolated hospital ward and were served food from the kitchen in the ward. Only in those who were deprived of thiamine did polyneuropathy develop. These conditions would seem to reduce the probability that toxic or infectious factors were the cause of the neuropathies observed. We have given thought to the possibility that thiamine deficiency may have decreased the factor of resistance and thereby caused the persons who had thiamine deficiency to become oversusceptible to infectious and toxic agents. This possibility, however, seems to be excluded in a recent paper.[8]

3. Simultaneously with the present study three other groups of subjects were maintained on a basal diet deficient in all factors of the vitamin B complex and known to be low in thiamine, riboflavin and niacin. By supplementation of the basal diet with crystalline vitamins of the B complex and with minerals and other nutrients isolated deficiencies of thiamine, of riboflavin, of nicotinic acid and of the vitamin B complex have been produced. Polyneuropathy has developed only in subjects who have been deprived of thiamine.

---

12. Leblond, C. P., and Chaulin-Serviniere, J.: Spontaneous Beriberi of the Monkey as Compared with Experimental Avitaminosis, Am. J. M. Sc. **203**:100-109 (Jan.) 1942.

SUMMARY

The quantity of thiamine in the diet of 2 human volunteers was restricted to 0.2 mg. per day (0.1 mg. for each 1,000 calories) for 120 days. A test dose of 1.0 mg. of thiamine hydrochloride was administered subcutaneously approximately every two weeks during this period of thiamine deprivation, thus raising the average daily intake of thiamine to a total of 0.35 mg. (0.175 mg. per thousand calories). Administration of the test dose of thiamine served as a "periodic partial cure" of the thiamine deficiency. Appetite would improve and activity would increase for 7 to 10 days after each injection.

Symptoms and signs of thiamine deficiency were manifested as early as the thirtieth day of restriction. The first objective evidence of abnormality in these subjects consisted of a decrease in their ordinary urinary excretion of thiamine. At about the fiftieth day the urinary excretion of thiamine after administration of a test dose of 1 mg. of thiamine hydrochloride was reduced. After this time whenever dextrose was given, abnormally high values for pyruvic acid and lactic acid in the blood were encountered. About this time, also, anorexia and weakness became more severe than they had been and the subjects made complaints of paresthesia of the legs. Later, objective evidence of dysfunction of nervous pathways was obtained, and after 110 days of restriction polyneuropathy became clearly apparent in both subjects. The neuropathy consisted of defects of the sensory nervous pathways, loss of tendon reflexes and paralysis of muscles of the legs. It responded to administration of large doses of thiamine, but only after many weeks, and in 1 case incompletely after four months of continuous treatment.[10a]

The earliest stages of thiamine deficiency were demonstrated by determination of excretion after administration of a test dose of thiamine hydrochloride. More advanced stages of deficiency were suggested by data on pyruvic acid and lactic acid in the blood after administration of dextrose—a "metabolic load" test. Advancing degrees of thiamine deficiency were suggested by progressively higher blood pyruvic acid curves after administration of dextrose. This metabolic load procedure has diagnostic significance in athiaminosis but cannot be regarded as specific or pathognomonic.

Polyneuropathy has been a manifestation of late rather than early, severe rather than mild, deficiency of thiamine, representing an anatomic defect which was only slowly reversible even when thiamine hydrochloride was administered intensively.

102 Second Avenue Southwest.

URINARY SEDIMENT IN VISCERAL ANGIITIS (PERIARTERITIS NODOSA, LUPUS ERYTHEMATOSUS, LIBMAN–SACKS "DISEASE")

QUANTITATIVE STUDIES

MARCUS A. KRUPP, M.D.
SAN FRANCISCO

In recent years many reports have appeared concerning a group of disorders featured by peculiar lesions of small arteries, namely, periarteritis nodosa, lupus erythematosus disseminata, Libman-Sacks "disease" and the syndromes described by Friedberg and Gross. The terminology used in referring to these varied conditions is much confused and is by no means certain, but some relation among them at least seems possible. In searching for a useful clinical designation for the entire group W. Dock suggested "visceral angiitis," and this term has been in common use in the Stanford clinic for the past few years.[1]

Although the occurrence of renal lesions in association with visceral angiitis is well known,[2] the reported studies on the urine[3] of

---

From the Department of Medicine, Stanford University School of Medicine.

1. My associates and I use this as a purely clinical designation, inasmuch as there are different views as to the interpretation of the lesions (see Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569 [Oct.] 1941).

2. (*a*) Keil, H.: Conception of Lupus Erythematosus and Its Morphologic Variants, with Particular Reference to "Systemic" Lupus Erythematosus, Arch. Dermat. & Syph. **36**:729 (Oct.) 1937. (*b*) Engman, M. F., Jr.: Early Acute Lupus Erythematosus, ibid. **35**:685 (April) 1937. (*c*) Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Tr. A. Am. Physicians **38**:46, 1923. (*d*) Gross, L., and Friedberg, C. K.: Nonbacterial Thrombotic Endocarditis: Classification and General Description, Arch. Int. Med. **58**:620 (Oct.) 1936. Friedberg, C. K., and Gross, L.: Nonbacterial Thrombotic Endocarditis Associated with Acute Thrombocytopenic Purpura, ibid. **58**:641 (Oct.) 1936. Friedman, C. K.; Gross, L., and Wallach, K.: Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, ibid. **58**:662 (Oct.) 1936. (*e*) Goeckerman, W. H.: Lupus Erythematosus as a Systemic Disease, J. A. M. A. **80**:542 (Feb. 24) 1923. (*f*) Ginzler, A. M., and Fox, T. T.: Disseminated Lupus Erythematosus: A Cutaneous Manifestation of a Systemic Disease (Libman-Sacks), Arch. Int. Med. **65**:26 (Jan.) 1940. (*g*) Rose, E., and Pillsbury, D. M.: Acute Disseminated Lupus Erythematosus—A Systemic Disease, Ann. Int. Med. **12**:951, 1939. (*h*) Symposium on Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **15**:675-688, 1940. (*i*) Reifenstein, E. C.; Reifenstein, E. C., Jr., and Reifen-

patients with this condition have not been adequate. A series of 21 cases encountered in the last two years has furnished an unusual opportunity to make exact quantitative studies of the urinary sediment by the methods of Addis. These studies have revealed some interesting and characteristic features of the sediment in visceral angiitis, and they form the basis of this report.

METHOD AND MATERIAL

Specimens of urine were collected according to the method of Addis.[4] It may be recalled that the purpose of this procedure is to preserve the formed elements by obtaining fresh concentrated acid urine and also to estimate the total numbers of casts and cells excreted in a standard period. By this means it is possible to make an accurate assay of the nature and the course of a renal lesion. After withdrawing from a specimen the amount of urine required for the Addis count the remainder was allowed to stand in the refrigerator for two or three hours; 30 to 60 cc. was then pipetted from the bottom of the receptacle and centrifuged. The sediment, resuspended in 0.5 to 1.0 cc. of urine, was studied. The types of cells and casts were recorded, and differential counts of the casts were made.

In each of the 21 cases the disorder was given a clinical diagnosis of one or another of the components of visceral angiitis already enumerated. The diagnosis was confirmed by autopsy or muscle biopsy in all but 4 cases; however, in these cases the condition was considered definite enough to permit inclusion in this series (table, group A, cases 6 and 9; group B, cases 1 and 4).

---

stein, C. H.: A Variable Symptom Complex of Undetermined Etiology with Fatal Termination, Including Conditions Described as Visceral Erythema Group (Osler), Disseminated Lupus Erythematosus, Atypical Verrucous Endocarditis (Libman-Sacks), Fever of Unknown Origin (Christian), and Diffuse Peripheral Vascular Disease (Baehr and Others), Arch. Int. Med. **63**:553 (March) 1939. (*j*) Curtis, A. C., and Coffey, R. M.: Periarteritis Nodosa: A Brief Review of the Literature and a Report of One Case, Ann. Int. Med. **7**:1345, 1934. (*k*) Harris, A. W.; Lynch, G. W., and O'Hare, J. P.: Periarteritis Nodosa, Arch. Int. Med. **63**:1163 (June) 1939. (*l*) Grant, R. T.: Observations on Periarteritis Nodosa, Clin. Sc. **4**:245, 1940.

3. (*a*) Bunim, J. J.: Lupus Erythematosus Disseminatus, Ann. Int. Med. **13**:1399, 1940. (*b*) Keith, N. M., and Rowntree, L. C.: A Study of the Renal Complications of Disseminated Lupus Erythematosus: Report of Four Cases, Tr. A. Am. Physicians **37**:487, 1922. (*c*) Rose, E., and Goldberg, L. C.: Visceral Lesions of Acute Disseminated Lupus Erythematosus, M. Clin. North America **19**:333, 1935. (*d*) Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of Peripheral Circulation Usually Associated with Lupus Erythematosus and Endocarditis, Tr. A. Am. Physicians **50**:139, 1935. (*e*) Snapper, I.: Kidney Trouble in Acute Lupus Erythematosus, in Berglund, H., and Medes, G.: The Kidney in Health and Disease, in Contributions by Eminent Authorities, Philadelphia, Lea & Febiger, 1935, pp. 433-439. (*f*) Stickney, J. M., and Keith, N. M.: Renal Involvement in Disseminated Lupus Erythematosus, Arch. Int. Med. **66**:643 (Sept.) 1940. (*g*) Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569 (Oct.) 1941.

4. Addis, T.: A Clinical Classification of Bright's Diseases, J. A. M. A. **85**: 163 (July 18) 1925.

RESULTS

Of the 21 cases, the urinary sediment was normal in 3 (table, group C). In 4 other cases the sediment was of the sort which may occur in association with any febrile illness or with arteriosclerosis (table, group B). But in 14 cases in which the diagnosis was verified and in which there was obviously a severe renal lesion a sediment of unusual type was encountered. Indeed, its characteristics are so specific that once observed such sediment becomes of great diagnostic value in cases of doubtful renal disease.

In order to make clear the significance of the findings in these cases of visceral angiitis a brief review of the types of sediment encountered in cases of glomerulonephritis is necessary, and for the purpose of this description the disease may be divided—somewhat diagrammatically—into three active stages. In the initial stage the urine contains numerous red blood cells and red cell casts. The second stage, that of tubular degeneration, is characterized by the presence of fat in the urine; this fat is contained as droplets in hyaline casts and in the epithelial cells of the tubules (so-called "oval fat bodies"). Red cells are present, but during this stage red cell casts are not usually seen, for the glomerulitis has abated. Large amounts of protein occur in the urine, and at the same time the concentration of protein in the serum may be low. The third stage is the terminal one, in which the flow of urine is so slow in some of the large collecting tubules that large casts, known as broad, or renal failure, casts, are formed. It is in this stage that hypertension and retention of urea in the blood become extreme. The presence of elements characteristic of the second and the third stage has often been observed in the same specimen of urine; the presence of those typical of the initial stage and the second stage has been observed in the same specimen only extremely rarely, in cases of fulminating disease, and the presence in one sample of urine of elements characteristic of all three stages has never been observed in a case of glomerulonephritis in the experience of the Stanford laboratory.

But in sharp contrast to the different sediments just outlined the urine in 14 of the 21 in this series presented in the same specimen red blood cells, red cell casts, oval fat bodies, fatty and waxy casts and, frequently, broad casts. In addition, abnormal quantities of protein were always present. Here, under one cover slip were seen elements characteristic of the three stages of glomerulonephritis, which are usually separated by years or decades. This unique microscopic picture we have come to refer to as that of the "urine of visceral angiitis." The data in these 21 cases are summarized in the table.

The finding of such a singular urinary sediment in cases of typical visceral angiitis became of diagnostic aid; when in later cases of atypical or obscure forms of the disease identical urinary sediments were

observed, further procedures which might otherwise have been neglected, such as muscle biopsy, were done in an attempt to confirm the diagnosis.

There is no obvious reason why this type of urinary sediment should never occur in an adult with rapidly progressing glomerulonephritis. Addis,[5] as a matter of fact, in reviewing his cases of glomerulonephritis found that he had encountered this picture on 2 occasions. However, his notes on these 2 cases of supposed glomerulonephritis show clearly that the patients really had disseminated lupus erythematosus. In 1 case (table, group A, case 14) in which the urine was typical of that of visceral angiitis the necropsy report was "subacute glomerulonephritis." The condition in this case, however, was suggestive clinically of periarteritis nodosa, with prolonged fever, arthralgia, myalgia, symptoms and signs referable to the central nervous system, cough and other difficulties referable to the respiratory tract, loss of weight and at autopsy polyserositis.

An attempt was made to correlate this singular urinary sediment with the microscopic renal changes. No quantitative relation was found. As a matter of fact, the renal lesion was often less severe than one would expect from the appearance of the sediment. Sometimes only minimal changes were observed in kidneys which discharged large numbers of formed elements. Qualitatively, however, the sediment can be explained by the histologic changes; the blood casts and hematuria, by the plugging of the capillaries of the tufts by hyalinized thrombi; the epithelial and fatty casts and the oval fat bodies, by the fatty degeneration of some of the convoluted tubules, and the broad casts, by the fact that in some lobules draining into a common collecting tubule system there had been fibrosis and hyalinization of many of the glomeruli. The other lesions, the relation of which to the sediment is doubtful or nonexistent, comprised crescents and synechiae partially obliterating Bowman's capsule and the thickening of the basement membrane of the capillary loops, or formation of lesions "wire loop." It is of interest that the only really typical "wire loop" lesions were encountered in a woman (table, group A, case 1) who clinically and pathologically had periarteritis nodosa rather than disseminated lupus erythematosus. There was no constant change in the vessels supplying the renal parenchyma. In those patients with normal urine no significant renal lesions were encountered.

The changes in the urinary sediment vary with the state of the patient, becoming more extreme during clinical exacerbation and lessening during remission, when its appearance may even suggest a latent stage of the renal disease. This is well illustrated by case 11, group A; after a particularly severe early phase of periarteritis nodosa the patient has improved greatly, and the changes shown in the table

5. Addis, T.: Personal communication to the author.

	Case Number	Age, Year	Sex	Duration of Illness	Quantitative Data on Urinary Sediment: Elements in Sediment of a Twenty-Four Hour Specimen of Urine: Casts, Millions	Types of Casts, Percentage of Total Number: Red Cells	Cellular Casts	Granular Casts	Waxy Casts	Hyaline and Fatty Casts	Broad Casts	Red Blood Cells, Millions	White Blood Cells and Epithelial Cells, Millions	Oval Fat Bodies, Millions	Protein, Gm.	Blood Urea, Mg./100 Cc.	Serum Protein, Gm./100 Cc.	CO_2-Combining Power of Plasma, Volumes per Cent	Blood Pressure, Mm. Hg	Cutaneous Lesions
	Normal limit.....				0.1	0	0	+	0	+	0	1.0	2.0	0	0.03	...	.....	..	.....	..
Group A	1	24	F	7 mo.	1.4 to 7.6	5 to 15	+	50	+	30	0 to 20	15 to 1,600	8 to 29	+++	1.2 to 6.0	18 to 300	? to 4.6	42	118/76 to 168/110	0
	2	21	F	24 mo.	0.2 to 8.6	0 to +++	+	+	+	+	+	9 to 600	5 to 1,200	0 to +	0.03 to 9.4	30 to 265	5.4	37 to 27	110/76	0
	3	41	F	10 mo.	0.8 to 3.4	10	12	25	5	+	+	12 to 295	13 to 306	6	0.3 to 2.2	27 to 115	4.9	43	176/112	+
	4	43	F	30 mo.	1.4 to 2.7	10	+	+	+	+	+	180	30	+	3.8	75 to 140	6.2 to 5.2	38	155/88 to 210/120	+
	5	42	F	3 mo.	2.1	30 to 40	5	30	10	5	5 to 10	7,000	1,400	+	1.7	170	4.2	..	125/85	0
	6	20	M	8 mo.	30	+	+	+	+	+	?	82	66	..	2.4 to 7.9	43 to 157	....	..	145/80	+
	7	57	F	10 mo.	1.4	15	+	+	+	+	..	560	218	..	2.6	66	...	..	135/80	0
	8	32	F	6 mo.	1.2	6	12	12	3	67	?	420	76	..	5.6	86	....	..	120/70	0
	9	45	F	16 mo.	5.1	6	13	24	11	42	4	47	45	1	0.5	46	....	..	145/95	0
	10	22	F	24 mo.+	4.5	3	5	24	12	56	..	21	18	2	0.3	...	....	..	100/60	0
	11	39	M	18 mo.+	3	..	+	+	+	+	..	525	600	..	4.5	140	5.3	..	160/100	+
					0.9	5	5	..	..	..	..	432	42	6	1.8	30	6.1	..	138/95	0
					0.4	..	..	..	..	..	..	28	3	..	0.7	31	6.88	..	163/125	0
					...	..	..	..	..	..	..	...	...	..	...	..	....	..	.....	0
	12	58	F	6 mo.+	0.5	+	+	..	+	+	..	425	250	..	1.3	30	....	..	115/70	+
	13	42	M	4 mo.	0.25	+	?	..	..	..	..	1.5	5.0	..	++	...	....	..	215/135	0
	14	57	M	8 mo.	0.7	10	17	20	15	38	..	1,800	143	123	3.3	57	....	..	105/60	0
Group B	1	28	F	7 mo.	0.1	..	..	..	..	+	..	2	8	..	0.1	..	....	..	104/72	+
	2	19	F	8 mo.	0.2	..	..	..	..	+	...	21	3	..	0.1	21	....	..	100/60	0
	3	56	M	1 mo.	0.3	..	..	..	..	..	..	10	16	..	2.14	178 to 53	....	..	115/80	0
	4	49	F	36 mo.+	0	..	..	..	..	..	..	10	3	..	0.2	..	....	..	122/80	0
Group C	1	52	M	40 mo.	0	..	..	..	..	..	..	0	0	..	0	22	6.4	..	115/85	+
	2	43	M	36 mo.	0	..	..	..	..	..	..	0	0	..	..	..	.....	..	.....	0
	3	23	F	11 mo.+	0	..	..	..	..	..	..	..	2	0	0	..	....	..	110/75	+

* The cases have been divided into three groups on the basis of urinary sediment: A, "typical"; B, nondescript, and C normal.

Clinical and Pathologic Data				
Necropsy				
Glomeruli	Tubules	Blood Vessels (Arterioles)	Libman-Sacks Endocarditis	Comment
.....	.....	.....	.....	.....
None normal; "wire loop" lesions present; fibrosis; some crescents	Fatty degeneration	Many arterioles with thick hyalinized walls; partial occlusion	.....	Clinically periarteritis nodosa; only case in series in which classic "wire loop" lesions present
Proliferation of Bowman's capsule; no crescents; thick individual loops	Normal	Some arterioles with marked medial necrosis and perivascular white blood cell collars	Nodules on tricuspid value; ? atypical	Periarteritis nodosa with renal lesions resembling, but not typical of, those of glomerulonephritis; urine of assistance in diagnosis
Fibrosis and increased cellularity of loops; some fibrin plugs in capillaries	Slight fatty degeneration	Normal	.....	Death due to pneumococcic sepsis; a case of severe lupus erythematosus disseminata
Some fibrosis and hyalinization; few crescents	Marked fatty degeneration	Only slight arteriolar thickening	Definite endocarditis with lesions on tricuspid and on mitral valve	Classic lupus erythematosus disseminata with Libman-Sacks endocarditis; no pericarditis; hypertension, heart failure, uremia terminally
.....	.....	.....	.....	Peculiar pneumonitis revealed by roentgen examination; pulmonary and renal diseases predominant; no autopsy; renal lesions of aid in diagnosis
.....	.....	.....	.....	Renal lesion the initial manifestation, followed by evidence of involvement of other organs in disseminated lupus erythematosus; one of Addis' cases in which the initial diagnosis in 1931 was glomerulonephritis
None normal; fibrosis; necrosis of media of arterioles	Fatty degeneration	Infiltration of adventitia with white cells; medial necrosis and thrombosis	Valve edges and chordae tendineae thickened?	Periarteritis nodosa with renal lesion; asthma was initial difficulty
Edematous	Edematous; fatty degeneration	.....	.....	Lupus erythematosus disseminata with renal lesions; diagnosis was glomerulonephritis in 1930; case discovered in review of Addis' files
"Nephritis"	.....	.....	.....	Autopsy elsewhere; unable to get complete examination to report
.....	.....	.....	.....	Muscle biopsy; subacute periarteritis, myositis; urine of aid in diagnosis
.....	.....	.....	.....	July 7, 1940; patient ill, pale, edematous; heart enlarged
.....	.....	.....	.....	Sept. 10, 1940: patient improved; peripheral neuritis; biopsy of muscle: periarteritis nodosa
.....	.....	.....	.....	Nov. 14, 1940: patient improved
.....	.....	.....	.....	March 13, 1941: patient improved; in August 1941 only trace of protein in urine
.....	.....	.....	.....	Muscle biopsy: periarteritis nodosa
Fibrosis and hyalinization	Fatty degeneration	Arterioles with hyalinized thick walls to point of occlusion	.....	Periarteritis nodosa proved
None intact; many hyalinized; many crescents	Fatty degeneration	Arteriolar walls thick	.....	Diagnosis of subacute glomerulonephritis at autopsy; clinically a clearcut case of periarteritis nodosa
.....	.....	.....	.....	Classic lupus erythematosus disseminata with cardiac murmur of possible valvular lesion
Normal	Normal	Normal	.....	Periarteritis nodosa with lesions of of heart and lung; pneumonia peculiar to periarteritis
Thick basement membrane of capillary loop; some hyalinized glomeruli	Fatty degeneration	Not remarkable	.....	Arterioles of heart, renal pelvis and other tissues infiltrated and surrounded by eosinophils
.....	.....	.....	.....	Diagnosis unconfirmed; clinically a case of visceral angiitis
Normal	Normal	Normal	Valvulitis with verrucae on chordae tendineae	Clinically disseminated lupus erythematosus, but at autopsy extensive periarteritis encountered; a case which constitutes evidence in favor of considering these diseases as common entities
.....	.....	.....	.....	Muscle biopsy: periarteritis nodosa
.....	.....	.....	.....	Clinically visceral angiitis; muscle biopsy: normal vessels, subacute myositis

are reflected in the urinary sediment. Similar variations were observed in case 12, group A.

Another point of interest is that not only the urinary sediment but at times the clinical picture showed simultaneously the features of early and late stages of glomerulonephritis. It was common, for example, to see a patient with hypoproteinemic edema (degenerative stage) and retention of urea and hypertension (terminal stage). In this series normal blood pressures were encountered not only in those cases in which the kidneys were not affected but also in 8 cases in which there were severe renal lesions (group A, cases 2, 5, 6, 7, 8, 10, 12 and 14), in some of which there were gross signs of renal failure. Normal blood pressures were also encountered in the cases of visceral angiitis during a stage of severe tubular degeneration, just as in the case of the "nephrotic" stage of ordinary nephritis. Hypertension, when it did occur, was with 1 exception always associated with renal failure.

Finally, there has been much speculation as to the relation of the various clinical syndromes which I have enumerated under the heading visceral angiitis.[6] On the other hand, I do not advance the similarity of the urinary sediments in these clinical states as a basis for the view that they are all variants of one disease entity. I cannot do that, because it is known that in diseases of entirely diverse causation and pathogenesis one may in the end find sediments that are indistinguishable.

When a renal lesion exists in visceral angiitis, it is of such a nature as to induce glomerular bleeding and the passage of fibrinogen through the glomerular membrane, with the formation of blood casts, fatty degeneration of tubule cells and local oliguria that leads to the formation of broad casts. There is thus a relation between the diseases grouped under this term, though it is not maintained that the renal lesions are histologically identical, still less that they have the same causation or pathogenesis. In case 1, group C, especially interesting in this connection, the patient showed the clinical features of lupus erythematosus, but at autopsy the classic lesions of periarteritis nodosa were revealed. In case 1, group A, also to the point, the clinical diagnosis was periarteritis, but at autopsy the "wire loop" glomerular lesions described in association with lupus erythematosus were found.

---

6. (*a*) Keil, H.: Dermatomyositis and Systemic Lupus Erythematosus: II. Comparative Study of Essential Clinicopathologic Features, Arch. Int. Med. **66**: 339 (Aug.) 1940. (*b*) Banks, B. M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? New England J. Med. **225**:433, 1941. (*c*) Denzer, B. S., and Blumenthal, S.: Acute Lupus Erythematosus Disseminatus, Am. J. Dis. Child. **53**:525 (Feb.) 1937. (*d*) Ginzler and Fox.[2f] (*e*) Rose and Pillsbury.[2g]

SUMMARY AND CONCLUSIONS

Twenty-one cases of periarteritis nodosa, lupus erythematosus disseminata, Libman-Sacks "disease" and the syndromes of Friedberg and Gross were studied with particular reference to the clinical manifestations of the renal lesion.

In 7 cases no specific changes in urinary sediment were discovered, but in 14 cases a singular picture of the sediment was observed. The uniqueness of this picture lies in the presence of red blood cells, red cell casts, oval fat bodies, fatty casts, broad casts and abnormal quantities of protein in the same specimen of urine. These elements do not occur together in association with glomerulonephritis or with any other renal lesion with which I am familiar.

This unusual sediment is of diagnostic value in doubtful cases of the disorders just mentioned.

The term visceral angiitis is advanced as a convenient clinical designation for these disorders and is not meant to imply a common etiologic relation.

Stanford University Hospitals.

EXCRETION OF COPROPORPHYRIN IN HEPATIC DISEASE

III. URINARY EXCRETION OF COPROPORPHYRIN IN HEPATIC INSUFFICIENCY DURING EPISODES CHARACTERIZED BY NEUROLOGIC MANIFESTATIONS

SAMUEL NESBITT, M.D.
Associate Physician, New Haven Hospital; Instructor in Medicine, Yale University School of Medicine
NEW HAVEN, CONN.

As stated in previous papers of this series,[1] it is probable that porphyrin arises within the body during the process of synthesis of hemoglobin, protoporphyrin III composing the prosthetic group of hemoglobin, myoglobin and various respiratory ferments,[2] and that porphyrin of isomeric series I, which arises as a useless by-product during this synthesis, as well as any porphyrin of isomeric series III that is not utilized, is excreted in the urine and feces as coproporphyrin. The total amount of coproporphyrin excreted as well as the ratio of urinary to fecal excretion depends chiefly on the rate of production of porphyrin and the efficiency of the liver, which is the more important organ of excretion of porphyrin, the kidneys normally excreting but

---

Abstract of a portion of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Ph.D. in Medicine.

1. Nesbitt, S., and Snell, A. M.: (*a*) The Excretion of Coproporphyrin in Hepatic Disease: I. Correlation of Urinary and Fecal Excretion with Parenchymatous Hepatic Damage, Arch. Int. Med. **69**:573-581 (April) 1942; (*b*) Excretion of Coproporphyrin in Hepatic Disease: II. Urinary and Fecal Excretion in Biliary Obstruction, ibid. **69**:582-588 (April) 1942.

2. (*a*) Dobriner, K.: Porphyrin Excretion in Feces in Normal and Pathological Conditions, J. Biol. Chem. **120**:115-127 (Aug.) 1937. (*b*) Dobriner, K., and Rhoads, C. P.: The Metabolism of Blood Pigments in Pernicious Anemia, J. Clin. Investigation **17**:95-103 (Jan.) 1938. (*c*) Dobriner, K.; Strain, W. H.; Localio, S. A.; Keutmann, H., and Stephens, D. I.: II. Coproporphyrin I Metabolism and Hematopoietic Activity,, Proc. Soc. Exper. Biol. & Med. **36**:755-756 (June) 1937. (*d*) Rimington, C.: Porphyrins and Their Relation to the Metabolism of Blood Pigments, Proc. Roy. Soc. Med. **32**:1268-1275 (Aug.) 1939. (*e*) Lemberg, R.: Transformation of Haemins into Bile Pigments, Biochem. J. **29**:1322-1336 (June) 1935.

a small fraction of the total porphyrin excreted.[3] It has been demonstrated that in the event of parenchymatous hepatic damage the ratio of urinary excretion to fecal excretion is increased roughly in proportion to the degree of hepatic dysfunction [1a] and that in obstruction of the biliary ducts this ratio is also increased in proportion to the degree of obstruction. When the continuity of the biliary passage is restored by operative means the normal ratio of urinary excretion to fecal excretion of coproporphyrin is restored, provided, of course, that the hepatic function is adequate.[1b]

Four patients who had severe alcoholic cirrhosis of the liver afforded an opportunity for study of the daily urinary excretion of coproporphyrin during repeated episodes of acute hepatic insufficiency which were evidenced by periods of neurologic manifestations ranging from mild disorientation and psychotic behavior to deep coma. Sometimes during such episodes choreiform movements occurred, and occasionally pathologic neurologic signs could be elicited, including a Babinski reflex and sustained ankle clonus. At such times there was a decline in urinary output, the patient might become cyanotic and a peculiar odor, which has been described as "mousy," might be noticed. During these periods the concentration of sugar and of electrolytes in the blood remained within normal limits. The records of these patients have been reviewed in detail by Snell and Butt.[4]

The patients were maintained on a meat-free diet throughout the period of study. On the basis of Mann and Bollman's [5] studies they were placed on a high carbohydrate, high nonmeat protein, low fat diet to which were added vitamin supplements.[4] In view of the interesting studies by Jolliffe and others,[6] intensive parenteral administration of vitamins was employed during the acute episodes. The vitamins administered included at least 100 mg. of nicotinic acid, 100 mg. of

3. Dobriner, K., and Rhoads, C. P.: The Quantitative Determination of Urinary Coproporphyrin, New England J. Med. **219**:1027-1029 (Dec. 29) 1938. Watson, C. J.: Concerning the Naturally Occurring Porphyrins: I. The Isolation of Coproporphyrin I from the Urine in a Case of Cinchophen Cirrhosis, J. Clin. Investigation **14**:106-109 (Jan.) 1935; Concerning the Naturally Occurring Porphyrins: IV. The Urinary Porphyrin in Lead Poisoning as Contrasted with That Excreted Normally and in Other Diseases, ibid. **15**:327-334 (May) 1936. Dobriner.[2a]

4. Snell, A. M., and Butt, H. R.: Hepatic Coma: Observations Bearing on Its Nature and Treatment, Tr. A. Am. Physicians **56**:321-329, 1941.

5. Mann, F. C., and Bollman, J. L.: Jaundice: A Review of Some Experimental Investigations, J. A. M. A. **104**:371-374 (Feb. 2) 1935.

6. Jolliffe, N.; Bowman, K. M.; Rosenblum, L. A., and Fein, H. D.: Nicotinic Acid Deficiency in Encephalopathy, J. A. M. A. **114**:307-312 (Jan. 27) 1940. Jolliffe, N.: Effects of Vitamin Deficiency on Mental and Emotional Processes, A. Research Nerv. & Ment. Dis., Proc. (1938) **19**:144-153, 1939.

thiamine chloride, 200 mg. of ascorbic acid and one of the preparations which possess vitamin K activity.[4] It is interesting that the patients did recover repeatedly from the acute episodes.

One of the patients was confused and disoriented when he entered the hospital, and he soon lapsed into deep coma, from which he roused. During a comparatively brief stay in the hospital he experienced one other period during which he was stuporous and semicomatose. Again he improved, and he left the hospital. Three of the patients were observed over long periods during which they experienced repeated episodes of acute hepatic insufficiency, in which the state ranged from confusion to deep coma. Two of the patients exhibited a Babinski reflex and sustained ankle clonus during some episodes. One patient suffered

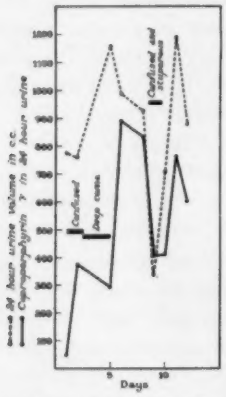


Chart 1 (case 1).—Excretion of urinary coproporphyrin.

a terminal hemorrhage from a ruptured varix. One patient died, mesenteric thrombosis having developed. One patient returned to his home and has continued to improve.

In each instance daily determinations of the urinary coproporphyrin excreted were made, and these are represented graphically in charts 1 to 4 along with the corresponding volumes of urine. The periods of acute hepatic insufficiency have been indicated. From this study several things became apparent. It was noted that the amount of coproporphyrin excreted in the urine was surprisingly parallel to the corresponding volume of urine. It was observed also that before and during each episode of acute hepatic insufficiency a sharp decline in the amount of urinary coproporphyrin as well as in the volume of urine occurred and that the values increased abruptly as the patient emerged from the acute episode.

The first patient (chart 1) on admission was disoriented, and he soon lapsed into deep coma. During this episode the amount of urinary coproporphyrin, although greater than the normal range of 0 to 100 gammas, was relatively low compared with the values for urinary coproporphyrin between the acute episodes. As the patient improved clinically, the value rose sharply. On the eighth day he experienced another such episode—he became confused and stuporous, and the volume of the urine and the urinary excretion of coproporphyrin again were diminished. The values again increased abruptly as he improved.

The second patient (chart 2) experienced five such episodes of acute hepatic insufficiency, and the same findings with regard to urinary volume and urinary coproporphyrin were noted. In this instance, on several occasions (as indicated by *a*) after the final episode of acute hepatic insufficiency a relatively low value

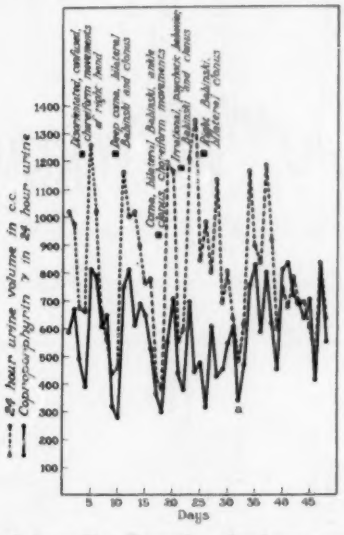


Chart 2 (case 2).—Excretion of urinary coproporphyrin.

for both urinary volume and excretion of coproporphyrin was observed; at these times the patient did not exhibit any untoward neurologic manifestations.

The third patient (chart 3) experienced eight episodes of acute hepatic insufficiency over a period of three months, with the usual changes in urinary volume and excretion of coproporphyrin. Similar low values were observed in several instances (indicated by *a* to *e*) without any clinical evidence of acute hepatic insufficiency.

The course of the fourth patient (chart 4), who was observed over a period of three months, was similar to that of the third patient. Eight episodes of acute hepatic insufficiency occurred, with the usual findings as to values for urinary volume and for urinary excretion of coproporphyrin. Again on several occasions (indicated by *a* to *e*) low values were observed in the absence of clinical evidence for acute hepatic insufficiency.

It has long been recognized that a diminished urinary output occurs before and during episodes of acute hepatic insufficiency and that there is an elevation of the nonprotein nitrogen content of the blood at such

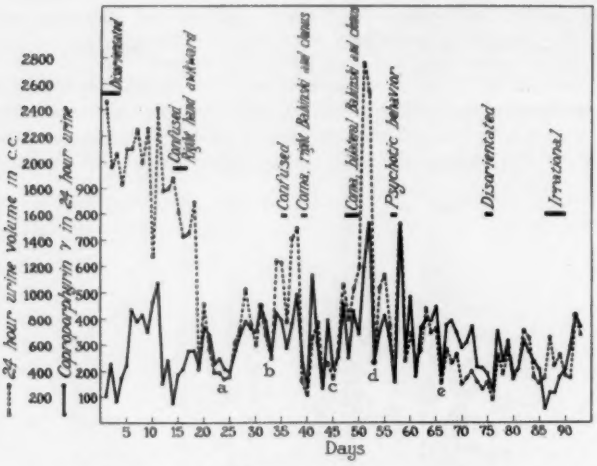


Chart 3 (case 3).—Excretion of urinary coproporphyrin.

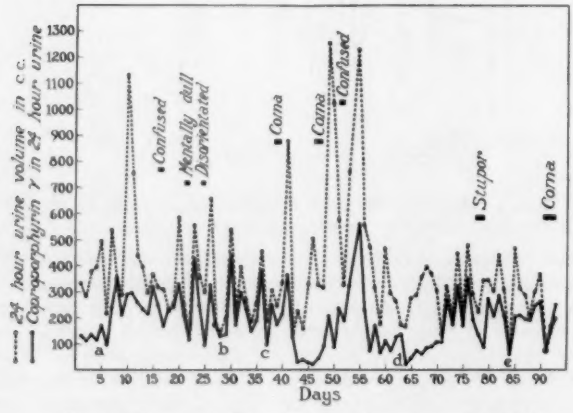


Chart 4 (case 4).—Excretion of urinary coproporphyrin.

times. Many workers have attributed these changes to failing renal function in addition to hepatic insufficiency, the acute picture thus being produced by the retention of hypothetic toxic substances. It is interesting to speculate as to what, if any, part retention of porphyrin may have to play in relation to these toxic substances.

SUMMARY AND CONCLUSIONS

In 4 cases of severe alcoholic cirrhosis of the liver it has been demonstrated that a close correlation exists between the values for urinary coproporphyrin excreted daily and for the corresponding urinary volume and that these values bear a definite relation to the onset and the course of periods of acute hepatic insufficiency. It seems fair to assume that the declining urinary excretion of coproporphyrin observed with the fall of urinary output before and during such periods is merely a reflection of a diminished renal function which occurs together with the diminished hepatic function at such times.

The Mayo Clinic.

ALKAPTONURIA WITH HYPERURICEMIA

ALAN LESLIE, M.D.
NEW YORK

Alkaptonuria is an unusual disease, but the metabolic disorder which it represents assumes considerable importance because of the light it sheds on the normal catabolism of two essential amino acids. The existence of the disease has apparently been known since the sixteenth century,[1] but only with the more recent knowledge of amino acid metabolism has its true nature been understood. It may be regarded as a deficiency disease, the deficiency probably being intrinsic rather than extrinsic. Although the deficient factor is not known, it is presumably a catalyst for a specific stage in the breakdown of tyrosine and phenylalanine. This will be considered later and in greater detail.

The clinical detection of alkaptonuria is usually simple. The most common history obtained is that of a peculiar blackening or darkening of an infant's urine-moistened diaper when it is exposed to air. Sometimes the urine is abnormally dark when voided. Occasionally, the condition is not noticed until later life, when a reducing substance which proves not to be sugar is detected by routine urinalysis. However, in this event the probability is that the condition has existed since birth. Several members of a family are commonly affected; instances of the disease among ancestors may be recalled. It is not apparent whether the disease tends more toward maternal or paternal transmission. No other symptoms are observed in alkaptonuria until relatively later in the course of the disease when ochronosis appears. This was first described by Virchow,[2] who did not associate it with alkaptonuria. Ochronosis is characterized by a bluish discoloration of the cartilages, most easily discernible in the ears and the alae nasi, and is due to the deposition of oxidation products of homogentisic acid. Albrecht [3] expressed the belief that this pigment resulted from the combination of homogentisic acid or one of its derivatives with chondromucin or chondroitin-sulfuric acid in the cartilages. Although there is a predilection for the cartilages, the abnormal pigmentation is occasionally visible in the skin and the nails and in pingueculae. A similar picture

From the medical service of Dr. George Baehr and the laboratories of the Mount Sinai Hospital.

1. Garrod, A. E.: Inborn Errors of Metabolism, ed. 2, London, Oxford University Press, 1923.

2. Virchow, R.: Ein Fall von allgemeiner Ochronose der Knorpel und knorpläpnlicher Theile, Virchows Arch. f. path. Anat. **37**:212, 1866.

3. Albrecht, H.: Ueber Ochronose, Ztschr. f. Heilk. **23**:366, 1902.

may be seen in chronic poisoning with phenol. Degenerative changes take place in the articular cartilages, with the production of a particularly disabling form of osteoarthritis. Erosion of the intervertebral disks causes osteitis deformans alkaptonuria, as described by Söderbergh [4] and noted by Osler [5] and Albrecht.[3] This presents the clinical picture of spondylitis but is characterized by the absence of vertebral bridging in roentgenograms. Ochronosis does not develop in all cases of alkaptonuria, but the incidence has been high enough to account for the varied therapeutic efforts, which, unfortunately, have met with little success to date. A false positive Wassermann reaction is not uncommonly associated with alkaptonuria. Söderbergh [6] reported a case in which the Wassermann reaction, which became negative after a course of therapy with mercury inunctions, again was positive after the patient ingested excess tyrosine. Syphilis was most unlikely in this case. Söderbergh called attention to the similarity of the bone changes to those occurring in Paget's disease, in which condition also the Wassermann reaction is occasionally positive.

In an excellent review Garrod [1] cited 3 of the earliest cases on record: In 1584 Scribonius told of a perfectly healthy schoolboy whose urine was black. In 1609 Schenck described the case of a monk with black urine, and in 1649 Zacutus Lusitanus wrote of black urine in a boy whose urine was unaffected by drastic measures but who achieved healthy manhood, black urine and treatment notwithstanding. In 1859 Bödeker [7] isolated from the urine of a patient with glycosuria a second reducing substance, which turned black on the addition of alkali. This he named "Alkapton." In 1861 [8] he first described and named the disease alkaptonuria. In 1886 Brune [9] reported the first case in America.

Bateson,[10] Punnett [11] and Garrod [12] presented evidence that alkaptonuria is a rare mendelian recessive character. In most of the cases described the condition was shown to be hereditary. Wolkow and

4. Söderbergh, G.: Ueber Ostitis deformans ochronotica, Neurol. Centralbl. **21**: 1362, 1913.

5. Osler, W.: The Pigmentation of Cartilages, Sclerotics, and Skin in Alkaptonuria, Lancet **1**:10, 1904.

6. Söderbergh, G.: Zur Klinik der Alkaptonurie, Nord. med. ark., 1915, vol. 48, no. 3 and no. 4.

7. Bödeker, C.: Ueber das Alcapton, Ztschr. f. rat. Med. **7**:130, 1859.

8. Bödeker, C.: Das Alkapton, Ann. d. Chem. u. Pharmacol. **117**:98, 1861.

9. Brune, T. B.: A Reducing Substance in Urine, Resembling Glucose, Boston M. & S. J. **115**:621, 1886.

10. Bateson, W., in Report of the Evaluation Committee of the Royal Society, London, 1902, no. 1, p. 133, note.

11. Punnett, R. C.: Mendelism in Relation to Disease, Proc. Roy. Soc. Med. (Epidemiol. Sect.) **1**:135, 1908.

12. Garrod, A. E.: Inborn Factors in Disease, New York, Oxford University Press, 1931.

Baumann [13] in 1891 identified the substance known as "alkapton" as homogentisic acid. In 1895 Baumann and Fränkel [14] were able to synthesize homogentisic acid and prove its formula. This work was corroborated later by Osborne [15] and Neubauer and Flatow.[16]

Wolkow and Baumann [13] demonstrated increased excretion of homogentisic acid after the ingestion of tyrosine by a subject with alkaptonuria. Falta and Langstein [17] showed this phenomenon to occur after the ingestion of phenylalanine as well. Both of these amino acids contain the benzene ring, which human beings do not synthesize and which patients with alkaptonuria apparently cannot break down. Gibson and Howard [18] administered tyrosine and a measured diet to a patient with alkaptonuria and noted the characteristic rise in excretion of homogentisic acid. They concluded that the disease is due to the incomplete catabolism of the aromatic fraction of tyrosine and phenylalanine. Papageorge and Lewis [19] were able to produce excretion of homogentisic acid by white rats by daily oral administration of *l*-phenylalanine (0.3 Gm. per hundred grams of body weight). Sealock and Silberstein [20] produced it by the administration of extra tyrosine to guinea pigs on diets deficient in vitamin C. The latter authors were able to repeat this experiment successfully on 2 normal human beings. However, as shown in a later report, Sealock and associates [21] were unable to affect the metabolism of homogentisic acid in a patient with alkaptonuria by the administration of ascorbic acid, although the urine no longer darkened on standing. Sealock and Silberstein suggested that vitamin C is the deficient factor in experimental alkaptonuria, while the missing factor in hereditary

13. Wolkow, M., and Baumann, E.: Ueber das Wesen der Alkaptonurie, Ztschr. f. physiol. Chem. **15**:228, 1891.

14. Baumann, E., and Fränkel, S.: Ueber die Synthese der Homogentisinsaure, Ztschr. f. physiol. Chem. **20**:219, 1895.

15. Osborne, W. A.: A New Synthesis of Homogentisic Acid, Proc. Physiol. Soc. London, 1903, p. xiii.

16. Neubauer, O., and Flatow, L.: Synthesen von Alkaptonsäuren, Ztschr. f. physiol. Chem. **52**:375, 1907.

17. Falta, W., and Langstein, L.: Die Entstehung von Homogentisinsaure aus Phenylalanin, Ztschr. f. physiol. Chem. **37**:513, 1903.

18. Gibson, R. B., and Howard, C. P.: A Case of Alkaptonuria with a Study of Its Metabolism, Arch. Int. Med. **28**:632 (Nov.) 1921.

19. Papageorge, E. T., and Lewis, H. B.: Comparative Studies of the Metabolism of the Amino Acids: VII. Experimental Alkaptonuria in the White Rat, J. Biol. Chem. **123**:211, 1938.

20. Sealock, R. R., and Silberstein, H. E.: The Control of Experimental Alkaptonuria by Means of Vitamin C, Science **90**:517, 1939.

21. Sealock, R. R.; Galdston, M., and Steele, J. M.: Administration of Ascorbic Acid to an Alkaptonuric Patient, Proc. Soc. Exper. Biol. & Med. **44**: 580, 1940.

alkaptonuria is as yet unknown. Papageorge, Frohlich and Lewis [22] produced a great increase in the urinary excretion of homogentisic acid in patients with alkaptonuria by the oral administration of phenylalanine, in amounts roughly equal to 70 per cent of the total amount theoretically obtainable by the complete conversion of phenylalanine. They expressed the belief that homogentisic acid was an intermediate product of normal protein metabolism. Butts, Dunn and Hallman[23] produced alkaptonuria by feeding phenylalanine to normal rats but were unable to do so by feeding tyrosine.

Temporary disappearance of alkaptonuria during a period of starvation in which there was associated ketone acidosis was reported by Katsch,[24] and Reinwein [25] demonstrated a lowering of homogentisic acid excretion in a patient on a low carbohydrate diet. Diaz, Mendoza and Rodriguez [26] could not influence the excretion of homogentisic acid by the administration of a high ketone diet, which resulted in ketosis. Complete carbohydrate deprivation had no effect. Lieb and Lanyar [27] produced ketosis by the administration of a low carbohydrate diet but also were unable to corroborate the work of Reinwein. These authors [28] also tried reducing the protein intake of a patient with alkaptonuria. The ratio of homogentisic acid excretion to nitrogen excretion remained constant, despite diminution of the latter. Braid and Hickmans,[29] studying an infant with alkaptonuria, found that after a thirty hour period of starvation during illness homogentisic acid disappeared from the urine and was not replaced by acetone. A case of temporary alkaptonuria was reported by Furniss.[30] The alkaptonuria disappeared on recovery from an attack of jaundice and perhaps merely represented a temporary disturbance in tyrosine metabolism.

---

22. Papageorge, E. T.; Frohlich, M. M., and Lewis, H. B.: Excretion of Homogentisic Acid After Oral Administration of Phenylalanine to Alcaptonuric Subjects, Proc. Soc. Exper. Biol. & Med. **38**:742, 1938.

23. Butts, J. S.; Dunn, M. S., and Hallman, L. F.: Studies in Amino Acid Metabolism: IV. Metabolism of *dl*-, Phenylalanine and *dl*-Tyrosine in the White Rat, J. Biol. Chem. **123**:711, 1938.

24. Katsch, G.: Alkapton und Aceton, Deutsches Arch. f. klin. Med. **127**: 210, 1918; **134**:59, 1920.

25. Reinwein, H.: Untersuchungen über die Alkaptonurie, Deutsches Arch. f. klin. Med. **170**:327, 1931.

26. Diaz, C. J.; Mendoza, H. C., and Rodriguez, J. S.: Alkapton, Aceton, und Kohlhydratmangel, Klin. Wchnschr. **18**:965, 1939.

27. Lieb, H., and Lanyar, F.: Alkaptonurie und Kohlhydratenziehung, Ztschr. f. physiol. Chem. **186**:119, 1929.

28. Lieb, H., and Lanyar, F.: Alkaptonurie bei minimaler Eiweisszufuhr, Ztschr. f. physiol. Chem. **186**:111, 1929.

29. Braid, F., and Hickmans, E. M.: Metabolic Study on an Alkaptonuric Infant, Arch. Dis. Childhood **4**:389, 1929.

30. Furniss, H. D.: Alkaptonuria, J. Mt. Sinai Hosp. **4**:720, 1938.

By the administration of thyroid Schmieding [31] caused a parallel increase in nitrogen excretion and homogentisic acid excretion in a 7 year old girl with alkaptonuria. When there was evidence of thyrotoxicosis, the excretion of homogentisic acid exceeded that of nitrogen, with the restoration of the former relation after withdrawal of the thyroid. This author expressed the belief that there was a congenital defect of an enzyme, perhaps of hepatic origin. Klein and Bloch [32] reported a possible temporary improvement in a patient with alkaptonuria after the injection of liver extract, with subsequent complete relapse. Diaz, Mendoza and Rodriguez [26] could not demonstrate any effect of liver extract in a patient with the disease nor could Mosonyi.[33] In the report of Mosonyi and of Diaz and associates favorable results from the use of ascorbic acid were described. Mosonyi reported relief of arthralgias, which recurred when the administration of ascorbic acid was stopped and liver extract was given and which were again relieved by the administration of ascorbic acid (150 mg. per day), with which was given adrenal cortex extract. Sealock, Galdston and Steele [21] were unable to demonstrate any effect from the administration of ascorbic acid up to 4 Gm. per day. Diaz and associates [26] suggested that ascorbic acid merely prevented the oxidation of alkapton in the urine, consequently avoiding blackening of the urine, with little true metabolic effect.

REPORT OF A CASE

P. H., an American-born white housewife aged 24, came to the outpatient department in February 1936, complaining of pain in the right sternoclavicular joint. She also stated that her under garments became blackened by her urine, of which she had been slightly incontinent since the delivery of her second child. The discoloration was not immediate, since the urine was light in color when voided. This urinary abnormality had been observed in the patient by her mother, who had noticed a blackening of her diapers after birth. There were no siblings. There was no familial history of any similar disturbance, the patient's mother being alive and having diabetes and her father having died of an abdominal neoplasm at the age of 44. The patient's 2 children had never had any urinary abnormalities or any other significant deviation from normal. The patient's past history was essentially irrelevant. She used no alcohol, tobacco or drugs.

Physical Examination.—The patient's general appearance was one of good health. She was moderately obese. The hair was of normal texture, and there were no signs of myxedema. There were numerous dental cavities. The thyroid was not enlarged. The heart and the lungs were normal to percussion and auscultation. The blood pressure was 110 systolic and 80 diastolic. There was a small umbilical hernia. There was no neurologic abnormality or any evidence of pig-

31. Schmieding, E.: Stoffwechseluntersuchungen bei kindlicher Alkaptonurie, Monatschr. f. Kinderh. **73**:216, 1938.

32. Klein, O., and Bloch, K.: Beseitigung der Alkaptonurie durch parenterale Zufuhr von Leberextrakten, Klin. Wchnschr. **15**:1684, 1936.

33. Mosonyi, L.: A propos de l'alcaptonurie, Presse méd. **47**:708, 1939.

mentation in the aural and nasal cartilages. There was a small cystocele, with incontinence after straining. The right sternoclavicular joint was red, swollen and tender, and there was limitation of abduction of the arm. A routine examination of the urine failed to reveal any abnormality. The Wassermann reaction of the blood was negative. Roentgen examination of the affected joint did not show any bony abnormality. A year later, after persistent joint pain, roentgen examination again failed to show any bony abnormality.

Despite careful dental attention there was no improvement. In 1937 a course of therapy with a preparation containing organic iodine and casein (activin) was ineffective. In 1939 more thoroughgoing laboratory studies were performed.

The urine was reported to contain alkapton bodies. The hemoglobin concentration was 77 per cent (Sahli). The white cell count was 6,500, with 59 per cent polymorphonuclear leukocytes (all segmented), 37 per cent lymphocytes, 2 per cent mononuclear leukocytes and 2 per cent eosinophils. There was some basophilic stippling of the red corpuscles. The erythrocyte sedimentation time was normal. Per hundred cubic centimeters the blood contained 12 mg. of urea nitrogen, 95 mg. of sugar, 210 mg. of cholesterol, 115 mg. of esterified cholesterol, 9.6 mg. of

Effect of the Administration of Ascorbic Acid on the Urinary Excretion of Homogentisic Acid by a Patient with Alkaptonuria

Date	Medication	Urine Excreted, Cc./24 Hr.	Homogentisic Acid Excreted, Gm./24 Hr.
3/10/40	None	2,600	9.62
3/17/40	300 mg. of ascorbic acid daily for 3 preceding days	2,150	6.83
3/20/40	None	2,370	10.70
4/17/40	300 mg. of ascorbic acid daily	2,100	6.91
4/22/40	300 mg. of ascorbic acid daily	1,750	6.48
4/23/40	300 mg. of ascorbic acid daily	1,900	6.46
6/19/40	None	1,700	9.14

calcium, 7.7 King-Armstrong units of phosphatase and 8.6 mg. of uric acid. The urine of each of the patient's 2 children was found to be free of alkapton bodies. The urine of the patient's mother, who had diabetes, contained a reducing substance, which turned out to be sugar and not homogentisic acid.

Course of Illness.—The patient began complaining of pain in the left sternoclavicular joint as well. Another roentgenogram, taken in September 1940, showed considerable formation of new bone above the right sternoclavicular joint, with the formation of a spur 3 cm. from the proximal end of the clavicle. The articular margin of the sternum was irregular and showed evidence of formation of new bone. The left sternoclavicular joint showed some evidence of osteoarthritis. The roentgenologist suggested that the changes on the right side were probably due to an osteoarthritic process.

On a second determination the blood level of uric acid was 7.9 mg. per hundred cubic centimeters. After the administration of tincture of colchicum seed up to tolerance the blood level of uric acid rose to 13.3 mg. per hundred cubic centimeters, probably because of mobilization, since it dropped back to 8.6 mg. per hundred cubic centimeters with abatement of the effect of the colchicum seed. After exhibition of the drug there was marked amelioration of the arthritic symptoms.

Metabolic Studies.—Because of the improvement after the administration of ascorbic acid reported by other authors it was decided to perform quantitative studies

of urinary excretion of homogentisic acid to determine any possible influence of vitamin C. The diet was not weighed but was kept approximately constant. The determinations of alkapton were made according to the silver reduction method of Baumann.[34] The accuracy of this method was supported by confirmatory results of determinations done according to the method of Lieb and Lanyar.[35] The results are summarized in the table.

While the patient was taking ascorbic acid, one determination of the total amount excreted in a single day yielded a value of 273 mg. The urine, which formerly darkened after standing several hours, did not become dark after standing seventy-two hours. However, the under garments continued to be blackened as before, when the patient was incontinent. The ingestion of ascorbic acid did not affect the blood level of uric acid, which was 7.9 mg. per hundred cubic centimeters during the period of vitamin medication, nor did it affect the arthritic symptoms. The tincture of colchicum seed did not affect the excretion of homogentisic acid. A short trial of administration of vitamin E did not produce either clinical or laboratory improvement.

At present the patient is improved, probably because of the tincture of colchicum seed which she is continuing to take periodically. Ascorbic acid (150 mg. per day) is also being taken in an attempt to avoid future ochronosis. The prescribed diet is low in purine.

COMMENT

Most of the clinical and experimental evidence at hand points to the existence of homogentisic acid as an intermediate product of normal protein metabolism. Gross [36] stated that normal serum destroys homogentisic acid, with the probable production of acetone. Thus, it is apparent why alkapton bodies cannot be recovered under ordinary circumstances. However, transient alkaptonuria has been noted in association with illness,[37] and established alkaptonuria has disappeared during periods of starvation.[38] Furthermore, alkaptonuria can be produced experimentally by feeding excessive amounts of phenylalanine.[19] One of Abderhalden's laboratory assistants excreted homogentisic acid for twenty-four hours after ingesting a large amount of tyrosine.

The diagram, adapted from Neubauer, illustrates the probable course of tyrosine catabolism.

Gross expressed the opinion that patients with alkaptonuria lack an enzyme which is responsible for the last step in the diagram. The breaking of the benzene ring is the essential characteristic of this transition. Administration of tryptophan does not alter the ratio of homogentisic

34. Baumann, E.: Ueber die Bestimmung der Homogentisinsaure in Alkaptonharn, Ztschr. f. physiol. Chem. **16**:268, 1892.

35. Lieb, H., and Lanyar, F.: Ueber die jodometrische Bestimmung der Homogentisinsaure in Harn, Ztschr. f. physiol. Chem. **181**:199, 1929.

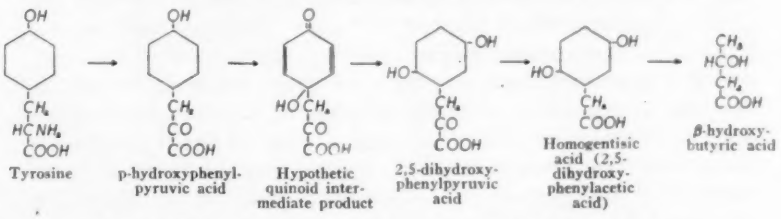
36. Gross, O.: Ueber der Einfluss des Blutserums des Normalen und des Alkaptonurikers auf Homogentisinsaure, Biochem. Ztschr. **61**:165, 1914.

37. Garrod.[1] Furniss.[30]

38. Katsch.[24] Braid and Hickmans.[29]

acid excretion: nitrogen excretion in patients with alkaptonuria. This fact seems to contravert Gross's contention, since this amino acid also contains a benzene ring. However, in this instance the benzene ring is part of the indole grouping, and its catabolism differs from that of tyrosine and of phenylalanine, which are the only parent substances of homogentisic acid.

It is true that the formulas shown represent merely a logical path of catabolism, without positive proof. The fact that even in patients with alkaptonuria the excretion of homogentisic acid is not quantitatively proportional to the ingested tyrosine or phenylalanine suggests a distorted, instead of an interrupted, catabolic pathway. However, this hypothesis does not consider the possibility of the utilization of these amino acids in protein synthesis or storage. The administration of ascorbic acid resulted in a decrease in alkapton excretion of roughly 30 per cent. Since the test employed was one involving silver reduction, the presence of vitamin C, a reducing agent, introduced an error, which,



The probable course of tyrosine catabolism (adapted from Neubauer).

if one considers the determination of ascorbic acid excretion, apparently did not exceed 5 per cent. It will be recalled that the darkening of the urine did not occur during the administration of ascorbic acid, although the under garments still were blackened. A similar observation was also made by Sealock and associates.[21] Although it appears that a true reduction in the excretion of homogentisic acid was effected, it is probable that the effect of vitamin C was merely secondary in the urine.

From the data presented, it is evident that although the administration of quantities of vitamin C well in excess of the estimated normal daily requirement appeared to lower the output of homogentisic acid, the fundamental distortion of metabolism was not affected. The apparent sparing action of vitamin C does not provide the answer to the question of the nature of the intrinsic deficiency. If it did, complete elimination of alkapton bodies from the urine would be expected.

It is tempting to speculate about a possible causative relation between the alkaptonuria and the hyperuricemia in the case presented. Because

of the favorable symptomatic response to tincture of colchicum seed, which was accompanied by alteration of the blood level of uric acid, it might be permissible to ascribe the hyperuricemia to the existence of true gout. But it is felt that there is insufficient evidence to justify such a claim. From what little is known of the two conditions, alkaptonuria and gout, there is some similarity of disease pattern. They are both apparently due to some specific intrinsic deficiency. There is abnormality of nitrogen metabolism in both, and in both there is destruction of cartilage and replacement by an abnormal metabolic deposit, severe joint manifestations occurring late in both diseases. However, beyond these superficial resemblances, the characteristics are divergent and need no elucidation here. If there were any significant causative relation, other cases of coexistent alkaptonuria and gout would surely have been described. A careful scrutiny of the literature failed to disclose a single additional case in which alkaptonuria and gout (or hyperuricemia) were coexistent. Ravold and Warren [39] reported a case in which they were able to demonstrate diminished urinary excretion of uric acid but gave no figures for blood levels of uric acid. They mentioned several authors who demonstrated apparent decreases in excretion of uric acid, as well as several who made no reference to such a decrease. No data on the blood were available to Ravold and Warren, and there were apparently no clinical manifestations to suggest gout. Adler [40] described a case in which excretion of uric acid remained constant during a rise in excretion of homogentisic acid. In the case described by Gibson and Howard [18] there was moderately high urinary excretion of uric acid, but no determination of the blood level of uric acid was made.

If there existed any fundamental relation between the alkaptonuria and the hyperuricemia in this case, any therapeutic attempt effective for one condition might have been expected to exert some effect on the other. This did not occur. Nevertheless, because it is reasonable to expect a common causation for the components of any syndrome, despite the lack of definite evidence for it in this case, the presence of two conditions reflecting distinct metabolic disorders in a single person may be more than an interesting coincidence.

SUMMARY

A case of alkaptonuria with hyperuricemia is presented. This is the first reported case in which these two conditions representing distinct metabolic disturbances have been coexistent. There was apparently no

39. Ravold, A., and Warren, W. H.: A Case of Alcaptonuria, J. Biol. Chem. **7**:465, 1910.

40. Adler, O.: Ueber Alkaptonurie, Biochem. Ztschr. **21**:5, 1910.

connection between the two disturbances, and laboratory studies and therapeutic efforts failed to reveal any.

Reduction in excretion of homogentisic acid was noted after the administration of ascorbic acid. It is probable that this was a secondary effect, because (*a*) ascorbic acid merely by virtue of its reducing properties can prevent darkening of the urine and (*b*) complete absence of homogentisic acid from the urine was not achieved.

Administration of ascorbic acid did not affect the blood level of uric acid, nor did administration of tincture of colchicum seed affect the excretion of homogentisic acid.

The mechanism of alkaptonuria is discussed.

Dr. M. Volterra performed the determinations of homogentisic acid.

111 East Seventy-Fifth Street.

EFFECT OF MASSIVE DOSES OF VITAMIN D ON CALCIUM AND PHOSPHORUS METABOLISM

OBSERVATIONS ON PATIENTS WITH ATROPHIC SPONDYLITIS AND WITH DEGENERATIVE ARTHRITIS OF THE SPINE

KARL P. KLASSEN, M.D.*
AND
GEORGE M. CURTIS, M.D.
COLUMBUS, OHIO

An adequate intake of vitamin D is essential for the optimal utilization of calcium and phosphorus in the normal metabolism of the human body. The minimal daily requirement is unknown, there being no conclusive experimental data on this subject. It is generally assumed that a daily intake of 300 to 600 U. S. P. units of vitamin D is sufficient. This is supplied to healthy persons by a well balanced diet and exposure to sunlight. In persons with chronic arthritis there may be inadequacy in both these factors. This has been suggested by Irons,[1] who recommended that the deficiency be met by increasing the intake of vitamin D. Buckley [2] advocated the use of cod liver oil as part of the general treatment of arthritis.

In recent years vitamin D has been used extensively in amounts greater than its physiologic requirement in the treatment of arthritis. It was originally so used in massive doses by Dreyer and Reed.[3] Different investigators have reported their experience with this form of therapy; however, the results have not been uniform. Some patients showed definite improvement, while in others there was no appreciable change. It is difficult to evaluate reported therapeutic results in chronic arthritis as there is no uniform method of recording the clinical changes. Spontaneous remissions and seasonal variations are known to occur.

Reports in the literature show a wide variation in the laboratory findings following massive dose therapy with vitamin D. Dreyer and Reed [3] found the serum calcium elevated to as high as 30 mg. per hun-

* Comly Fellow in Research Surgery.
From the Department of Research Surgery, Ohio State University.

This investigation was aided by a grant from Mr. William Wallace Kincaid, Ellerslie-on-Niagara, Youngstown, N. Y.

1. Irons, E. E.: Chronic Arthritis: A General Disease Requiring Individualized Treatment, Ann. Int. Med. **9**:1695 (June) 1936.

2. Buckley, C. W.: Prognosis in Arthritis, Lancet **1**:1023 (May 2) 1936.

3. Dreyer, I., and Reed, C. I.: Treatment of Arthritis with Massive Doses of Vitamin D, Arch. Phys. Therapy **16**:537 (Sept.) 1935.

dred cubic centimeters, while Wyatt and his associates [4] reported an increase of only 0.75 to 0.95 mg. per hundred cubic centimeters. In many cases of atrophic arthritis there was a subsequent decrease in the sedimentation rate. Steck [5] reported that increased bone density was noted after the administration of vitamin D to patients with atrophic arthritis. No changes were observed by Vrtiak and Lang.[6] The last-named authors, moreover, noted signs of toxicity in all their patients receiving massive doses. In a large series of cases Steck and his associates [7] observed toxic effects in 8 per cent of their patients. Dreyer and Reed [3] failed to find any relation between high serum calcium and toxicity. No complete studies of calcium and phosphorus metabolism were included in the previous reports concerning the effects of high levels of vitamin D in patients with chronic arthritis.

There is extensive literature on the subject of vitamin D and its relation to calcium and phosphorus metabolism. Most studies were made on experimental animals, while data on normal human subjects are incomplete. Albright and Sulkowitsch [8] reported the effect of massive doses of vitamin D on calcium and phosphorus metabolism in 3 patients with hypoparathyroidism. They concluded that the main action of vitamin D is to increase the absorption of calcium from the intestinal tract, with resultant secondary changes in the phosphorus metabolism.

Minor changes encountered in the bones of patients with chronic arthritis have led different investigators to the conclusion that there may be a disturbance in calcium and phosphorus metabolism in this disease. There is no known dysfunction of the parathyroids associated with chronic arthritis. Ropes and associates [9] failed to find any primary disturbance in calcium and phosphorus metabolism in patients with degenerative and with atrophic arthritis.

---

4. Wyatt, B. L.; Hicks, R. A., and Thompson, H. E.: Massive Doses of Vitamin D in the Treatment of Proliferative Arthritis, Ann Int. Med. **10**:534 (Oct.) 1936.

5. Steck, I. E.: Clinical Experience in the Treatment of Arthritis with Massive Doses of Vitamin D, Illinois M. J. **71**:243 (March) 1937.

6. Vrtiak, E. G., and Lang, R. S.: Observations on the Treatment of Chronic Arthritis with Vitamin D, J. A. M. A. **106**:1162 (April 4) 1936.

7. Steck, I. E.; Deutsch, H.; Reed, C. I., and Struck, H. S.: Further Studies on Intoxication with Vitamin D, Ann. Int. Med. **10**:951 (Jan) 1937.

8. Albright, F., and Sulkowitsch, H. W.: The Effect of Vitamin D on the Calcium and Phosphorus Metabolism: Studies on Four Patients, J. Clin. Investigation **17**:317 (May) 1938.

9. Ropes, M.; Short, C. L.; Rossmeisl, E., and Bauer, W.: Calcium and Phosphorus Metabolism in Rheumatoid and Degenerative Arthritis, J. Clin. Investigation **16**:675 (July) 1937.

An increased loss of calcium has been demonstrated in the majority of patients with hyperthyroidism.[10] Basal metabolic rates were studied in a number of patients with chronic arthritis by Pemberton and Tompkins [11]; Cecil, Barr and DuBois [12]; Hench [13] and, more recently, Rawles and his associates.[14] They reported the basal metabolic rate was within the limits of normal in the majority of the patients investigated. The incidence of low basal metabolic rates was greater in patients with degenerative arthritis. In patients with active atrophic arthritis there was a slight elevation of the basal metabolic rate.

A number of selected patients have been treated with massive doses of vitamin D in our clinic, but uniform results have not been obtained. By placing certain of these patients in the hospital under controlled management and studying their calcium and phosphorus metabolism, an attempt was made to determine certain of the actual metabolic changes produced by massive doses of vitamin D. We were also interested in possible changes produced by such treatment in the function of the parathyroids and the thyroid.

METHOD AND MATERIAL

The 4 patients selected for this investigation all had chronic arthritis of the spine. Their ages varied from 28 to 71 years. The 2 younger patients, E. M. and A. G., had active atrophic spondylitis, while the 2 older ones, J. C. and M. C., had degenerative arthritis of the spine. The essential features of the histories, as well as the results of physical and laboratory examination, are summarized in the case reports. The nature and the purpose of this investigation were explained to the patients, and all 4 cooperated well in the collection of specimens.

The routine methods employed were used by Puppel and Curtis.[10a] The calcium and the phosphorus intake was maintained at a relatively low level by eliminating foods with a high content of these elements; nevertheless, a palatable diet was provided, such as would be tolerated by the patients over the long periods of investigation. The patients ate all their food, and there was no change in the individual diet during the thirty-six days of observation. Distilled water was used and its daily intake maintained at a constant level. Sedatives and analgesics were employed occasionally. The drugs given did not contain calcium or phosphorus. During the investigation the patients were up and about the ward.

10. (*a*) Puppel, I. D., and Curtis, G. M.: Calcium and Iodine Metabolism in Thyroid Disease, Arch. Int. Med. **58**:957 (Dec) 1936. (*b*) Puppel, I. D.; Klassen, K. P., and Curtis, G. M.: The Calcium Metabolism in Thyroid Disease, West. J. Surg. **48**:374 (June) 1940.

11. Pemberton, R., and Tompkins, E. H.: Studies on Arthritis in the Army Based on Four Hundred Cases: II. Observations on the Basal Metabolism, Arch. Int. Med. **25**:241 (April) 1920.

12. Cecil, R. L.; Barr, D. P., and DuBois, E. F.: Clinical Calorimetry: XXXI. Observations on the Metabolism of Arthritis, Arch. Int. Med. **29**:583 (April) 1935.

13. Hench, P. S.: Systemic Nature of Chronic Infectious Arthritis, Atlantic M. J. **28**:425 (April) 1935.

14. Rawles, W. B.; Reese, A. A.; Gruskin, B., and Gordon, A. S.: Thyroid Activity in Chronic Arthritis, Ann. Int. Med. **11**:1401 (Feb.) 1938.

The investigation of each of the 4 patients was maintained for thirty-six days. This was subdivided into three main divisions, each of four three day periods. The control period constituted twelve days. This was followed by twelve days during which the patients were given a high vitamin D intake. The preparation used in these studies was an activated ergosterol[15] assayed to contain 50,000 U. S. P. units of vitamin D per capsule. The initial daily dose of 200,000 units was increased to 400,000 during the second three day period, then to 600,000 and 1,000,000 units daily, during the third and the last three day period, respectively. No vitamin D was given during the last twelve days of investigation.

The basal metabolic rate was determined on the morning of the first day of each period. A specimen of blood was drawn the same morning while the subject was fasting and analyzed within a few hours. The serum calcium was determined by the Clark and Collip[16] method and the inorganic phosphorus and the serum phosphatase by the methods of King.[17] The total calcium content of the food, feces and urine was determined by the method of Puppel and Curtis,[10a] while the total phosphorus content was determined by a modification of the King[17a] method. All specimens were analyzed in duplicate, and analyses were repeated when adequate checks were not obtained.

CASE 1.—*History.*—M. C., a 57 year old white housewife, was admitted to the hospital on Dec. 28, 1937. Approximately eight years prior to admission severe pain had developed in her hands and feet. This was followed by pain in her back and shoulders. Her discomfort was relieved by salicylates. In 1935 she had had an attack of acute pain in the upper right quadrant of the abdomen, not associated with jaundice. This condition was given the diagnosis of acute cholecystitis. She had had an appendectomy at the age of 25 and a hysterectomy at 35.

Physical Examination.—The patient was pale and somewhat emaciated. There was limitation of motion in the entire spine, particularly in the cervical portion. The spinal muscles were spastic and hypertrophied. The reflexes were normal.

Laboratory Examination.—The hemoglobin content was 13.6 Gm. per hundred cubic centimeters, with a red cell count of 4,820,000. The sedimentation rate was 0.3 mm. per minute. The total white cell count was 4,000, with a normal differential count. The blood level of urea nitrogen was 14 mg. per hundred cubic centimeters. There was a trace of albumin in the urine. The Wassermann reaction and the Kahn reaction were negative. The icteric index was 6. An intravenous

15. The preparation employed was ergosterol activated by the Whittier method (electrical activation of heat-vaporized ergosterol). This preparation (ertron, supplied for this investigation by the Nutrition Research Laboratories, Inc., Chicago) has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association. There have been published claims that it is less toxic in equivalent doses than are other preparations of activated ergosterol. These claims have, however, been questioned (Freyberg, R. H.: Treatment of Arthritis with Vitamin and Endocrine Preparations, J. A. M. A. **119**:1165 [Aug. 8] 1942. Freeman, S.: Irradiated Ergosterol Poisoning, Correspondence, ibid. **119**: 968 [July 18] 1942).

16. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461 (March) 1925.

17. (*a*) King, E. J.: The Colorimetric Determination of Phosphorus, Biochem. J. **26**:292, 1932. (*b*) King, E. J.; Haslewood, G. A. D., and Delory, G. E.: Micro-Chemical Methods of Blood Analysis, Lancet **1**:886 (April 10) 1937.

cholecystogram showed a normal gallbladder. Roentgen examination revealed lipping of the vertebral bodies of the entire spine, most marked in the dorsal portion. The intervertebral spaces were narrowed, and the vertebral bodies showed rarefaction. The apophyseal joints were normal. There was extensive calcification of the abdominal aorta.

Diagnosis.—The diagnosis was degenerative arthritis of the spine.

Course of Illness During Hospitalization.—This patient did not show any improvement while in the hospital. Salicylates and codeine were given for the relief of pain. No changes were noted in the blood, and the blood level of urea nitrogen was 15 mg. per hundred cubic centimeters at the time of discharge from the hospital. Roentgenograms taken five months later were not appreciably different from the initial ones.

CASE 2.—*History.*—E. M., a 28 year old white farmer, was admitted to the hospital on March 1, 1938. At the age of 18 he had experienced pain and swelling in his ankles. This lasted about a year and was followed by involvement of both knees. At the age of 20 he had become aware of pain and stiffness in both hips and in the lower portion of his back. The stiffness progressed, and gradually over a period of six years the entire spine had become involved. Marked forward bowing occurred and was associated with sharp radiating pain in his back. The limitation of motion in his hips also progressed, and during the two years before admission both shoulders had become involved. There was no history of severe illness. The patient stated he had never had a syphilitic or a gonorrheal infection. He had had a partial thyroidectomy for nontoxic nodular goiter at the age of 25.

Physical Examination.—The patient was pale and emaciated and walked with a waddling gait. Chest expansion was limited, and breathing was diphragmatic. There was a systolic murmur. The heart was normal in size. The patient had moderate kyphosis, with complete fusion of the spine up to the middorsal region and little motion in the upper dorsal and the cervical portion of the spine. The motion in both shoulders and hips was greatly reduced in all directions, and there was pain on forced motion. The reflexes were normal.

Laboratory Examination.—The hemoglobin content was 14.0 Gm. per hundred cubic centimeters, with a red cell count of 4,450,000. The sedimentation rate was 1.4 mm. per minute. The white cell count was 8,000, with an essentially normal differential count. The blood level of urea nitrogen was 15.0 mg. per hundred cubic centimeters. The Wassermann reaction and the Kahn reaction were negative. The urine was normal. Roentgenograms showed extensive calcification of the anterior and the lateral ligaments of the vertebral bodies and moderate kyphosis of the spine, without narrowing of the intervertebral spaces. The apophyseal and the sacroiliac joints were completely obliterated. The articulation of the os pubis at the symphysis was completely calcified. The articular spaces of the hip joints were normal, with lipping of the rim of the acetabulum. There was obliteration of the costovertebral joints.

Diagnosis.—The diagnosis was atrophic spondylitis.

Course of Illness During Hospitalization.—During the administration of vitamin D the patient's appetite increased and he had less pain. There ensued 10 per cent more motion in his hips, with some resultant improvement in his gait. On April 16 the sedimentation rate of the blood had decreased to 0.6 mm. per minute. No other changes in the blood were noted.

CASE 3.—*History.*—J. C., a 71 year old white retired salesman, was admitted to the hospital on March 4, 1938. When he was 69, radiating pain had developed in his right shoulder and elbow. This was partially relieved by salicylates. Four months prior to admission he noticed sensory disturbances in his left arm and in his shoulders, associated with stiffness and pain in his neck. These symptoms were present continuously and were not related to exertion. The past history was noncontributory.

Physical Examination.—The patient was slightly obese. There was limitation of motion in his neck and in his left shoulder.

Laboratory Examination.—The red cell count was 5,400,000, with a hemoglobin content of 16.7 Gm. per hundred cubic centimeters. The sedimentation rate was 0.2 mm. per minute. The total white cell count was 4,700, with a normal differential count. The urine was normal. The Wassermann reaction and the Kahn reaction were negative. The blood level of urea nitrogen was 14 mg. per hundred cubic centimeters. Roentgenograms revealed marked lipping of the entire spine, most evident in the cervical portion. The intervertebral spaces were narrowed. The apophysial joints were normal. There was complete calcification of the anterior ligaments of several vertebral bodies.

Diagnosis.—The diagnosis was degenerative arthritis of the spine

Course of Illness During Hospitalization.—There was no great change in the symptomatology throughout the patient's stay in the hospital. The attacks of pain did become less severe and less frequent. There was no change in the blood picture, and the blood level of urea nitrogen remained the same. No change was noted in the roentgen appearance of the spine.

CASE 4.—*History.*—A. G., a 31 year old white farmer, was admitted to the hospital on Dec. 1, 1937. He had been normal up to the age of 18, when for about three months he had suffered with acute pain and swelling in various joints of his body. This condition had then improved, and he had remained symptom free until the age of 23. At that time he had noted sharp, radiating pain in the lower portion of his back and in his hips. Associated with this was a progressive stiffening of the lower portion of his back, which had gradually ascended to involve the entire spine. His back had become fixed in a bent-forward position, and he had become unable to do his farm work because of the pain and deformity. The hip joints were stiff, but the bones did not fuse. The patient stated that he had not had any syphilitic or gonorrheal infection.

Physical Examination.—The patient was somewhat emaciated and walked with a waddling gait. The thoracic cage was fixed and flattened, and breathing was diaphragmatic. The extremities were normal except for the limitation of motion in both hips, with pain on forced motion. The reflexes were normal. There was marked kyphosis of the entire spine, with the maximum curvature in the dorsal portion. The entire spine appeared to be completely fused.

Laboratory Examination.—The hemoglobin content was 14.1 Gm. per hundred cubic cemtimeters, with a red cell count of 5,200,000. The sedimentation rate was 0.7 mm. per minute. The white cell count was 7,650 with a normal differential count. The blood level of urea nitrogen was 14.0 mg. per hundred cubic centimeters. The urine was normal. The Wassermann reaction and the Kahn reaction were negative. Roentgenograms revealed a "bamboo" type of spine, with calcification of the longitudinal ligaments, thinning of the intervertebral spaces and rarefaction of the vertebral bodies. There was complete fusion of the apophysial and the sacroiliac joints. The articular spaces of the hip joints were narrowed and presented cystic and sclerosing changes in the acetabulum and the head of the femur. There was lipping of the acetabular rim.

Diagnosis.—The diagnosis was atrophic spondylitis.

Course of Illness During Hospitalization.—During and also following administration of vitamin D there ensued improvement in the patient's appetite. He noted less pain and there was improvement in his gait. On Jan. 18, 1938 the sedimentation rate of the blood was 0.9 mm. per minute. There was no other change in the blood picture. Roentgenograms revealed no change from those taken on admission.

EXPERIMENTAL RESULTS

Control Period.—Daily samples of food taken from that served to the patients and analyzed at different intervals throughout the entire period of investigation showed the average calcium intake to range from 0.930 to 1.588 Gm. per three day period. On this intake the calcium balance remained negative in all 4 patients during the twelve day control period (tables 1 and 2, figs. 1 and 2). This negative balance was most evident in M. C., averaging 0.558 Gm. on an average three day intake of 0.930 Gm. The lowest average negative balance occurred in A. G., 0.178 Gm. on an intake of 1.4 Gm. of calcium per three day period. This increased total excretion over the intake of calcium is normal for patients maintained on a low calcium intake.

The phosphorus intake in the food was fairly constant in all 4 patients. The lowest three day intake was that of M. C., 1.924 Gm. The highest intake was that of E. M., 2.235 Gm. per three day period. The negative balance shown (tables 1 and 2) in these patients is normal. The highest negative phosphorus balance occurred in E. M., 0.339 Gm. (table 2). J. C.'s (fig. 1) intake and output were approximately equal.

The urinary excretion of calcium during the control period was within normal limits in all 4 patients. There was considerable individual variation which was not directly related to the amount of calcium ingested in the food. The highest excretion per period, 0.502 Gm., was that of A. G. (fig. 2). The excretion by E. M., on a higher calcium intake, was 0.075 Gm. (table 2). The fecal excretion of calcium was higher than the intake for 3 patients. A. G.'s fecal excretion was low, 1.076 Gm., while the high urinary excretion compensated and was mainly responsible for the negative balance.

The excretion of phosphorus in the urine was normal in all 4 patients. The lower values were obtained on the older patients. It varied from 1.221 to 1.640 Gm. per three day period. The fecal excretion of phosphorus was much lower than the urinary loss. It was related to the phosphorus intake in the food.

The serum calcium was slightly higher in the patients with atrophic spondylitis. In the same patients there was a fluctuation of about 5 per cent in the different determinations made during the control period.

TABLE 1.—*Metabolic Data on a Patient with Degenerative Arthritis of the Spine* *

Period	Date Period Started	Vitamin D, No. of U. S. P. Units per Day	Calcium, Gm.					Phosphorus, Gm.					Blood			
			Output			Intake in Food	Balance	Output			Intake in Food	Balance	Serum Calcium, Mg./100 Cc.	Serum Phosphorus, Mg./100 Cc.	Serum Phosphatase, King Units/100 Cc.	Basal Metabolic Rate, Percentage
			Urine	Feces	Total			Urine	Feces	Total						
1	1/ 8/38	.....	0.124	1.435	1.559	0.930	−0.629	1.235	0.865	2.100	1.924	−0.176	9.5	4.2	5.9	0
2	1/11/38	.....	0.184	1.349	1.533	0.930	−0.603	1.121	0.815	1.936	1.924	−0.012	9.7	4.3	9.0	+ 3
3	1/14/38	.....	0.182	1.320	1.502	0.930	−0.572	1.180	0.742	1.922	1.924	0.002	9.8	4.2	10.5	— 5
4	1/17/38	.....	0.157	1.199	1.356	0.930	−0.426	1.350	0.623	1.973	1.924	−0.049	9.7	3.4	11.0	— 3
Average for entire period.....			0.162	1.326	1.488	0.930	−0.558	1.221	0.761	1.982	1.924	−0.058	9.7	4.0	9.1	— 1
5	1/20/38	200,000	0.187	1.419	1.606	0.949	−0.657	1.323	0.842	2.165	1.939	−0.226	10.5	4.0	11.0	−11
6	1/23/38	400,000	0.266	0.787	1.053	0.968	−0.085	1.080	0.469	1.549	1.954	0.405	9.3	4.2	6.0	+ 3
7	1/26/38	600,000	0.355	1.169	1.524	0.986	−0.538	1.316	0.679	1.995	1.968	−0.027	9.2	4.2	15.5	— 8
8	1/29/38	1,000,000	0.693	0.595	1.288	1.024	−0.264	1.408	0.467	1.875	1.998	0.123	10.0	4.2	13.5	— 8
Average for entire period.....			0.375	0.992	1.367	0.982	−0.385	1.282	0.614	1.896	1.965	0.069	9.7	4.2	12.5	— 6
9	2/ 1/38	.....	0.758	0.755	1.513	0.930	−0.583	1.542	0.442	1.984	1.924	−0.060	9.6	4.6	8.5	0
10	2/ 4/38	.....	0.795	0.689	1.484	0.930	−0.554	1.074	0.600	1.674	1.924	0.250	9.7	4.5	11.2	+ 3
11	2/ 7/38	.....	0.700	0.516	1.216	0.930	−0.286	1.545	0.416	1.961	1.924	−0.037	10.1	5.0	13.4	— 3
12	2/10/38	.....	0.677	0.776	1.453	0.930	−0.523	1.079	0.630	1.709	1.924	0.215	8.3	4.5	14.0	— 5
Average for entire period.....			0.732	0.684	1.416	0.930	−0.486	1.310	0.522	1.832	1.924	0.092	9.4	4.6	11.7	— 1

* Patient M. C., a woman aged 57. The diet supplied 2,103 calories and 44 Gm. of protein. A high vitamin D intake was followed by increased urinary excretion, decreased fecal excretion and a diminished negative balance of calcium and of phosphorus. There was a slight rise in the serum inorganic phosphorus, without any appreciable change in the serum calcium.

TABLE 2.—*Metabolic Data on a Patient with Atropic Spondylitis* *

Period	Date Period Started	Vitamin D, No. of U. S. P. Units per Day	Calcium, Gm.					Phosphorus, Gm.					Blood			
			Output			Intake in Food	Balance	Output			Intake in Food	Balance	Serum Calcium, Mg./100 Cc.	Serum Phosphorus, Mg./100 Cc.	Serum Phosphatase, King Units/100 Cc.	Basal Metabolic Rate, Percentage
			Urine	Feces	Total			Urine	Feces	Total						
1	3/11/38	.....	0.082	1.785	1.867	1.588	—0.279	1.524	0.937	2.461	2.235	—0.226	10.4	5.3	8.5	+12
2	3/14/38	.....	0.071	1.752	1.823	1.588	—0.235	1.680	0.966	2.646	2.235	—0.411	9.9	5.2	8.3	+21
3	3/17/38	.....	0.067	1.933	2.000	1.588	—0.412	1.669	0.977	2.646	2.235	—0.411	9.9	4.1	9.0	— 3
4	3/20/38	.....	0.085	1.698	1.783	1.588	—0.195	1.689	0.857	2.546	2.235	—0.311	10.1	4.5	8.0	+ 8
Average for entire period.....			0.075	1.792	1.867	1.588	—0.279	1.640	0.934	2.574	2.235	—0.339	10.1	4.8	8.4	+ 9
5	3/23/38	200,000	0.093	1.611	1.704	1.607	—0.097	1.253	0.901	2.154	2.250	—0.096	9.8	4.7	6 2	+ 4
6	3/26/38	400,000	0.089	1.604	1.693	1.626	—0.067	1.603	0.875	2.478	2.265	—0.213	9.8	4.7	4.2	+11
7	3/29/38	600,000	0.162	1.061	1.223	1.645	0.422	1.345	0.544	1.889	2.280	0.391	9.8	4.6	6.0	+ 1
8	4/ 1/38	1,000,000	0.336	1.756	2.092	1.683	—0.409	1.760	0.913	2.673	2.310	—0.363	11.0	5.1	8.0	+ 5
Average for entire period.....			0.170	1.508	1.678	1.640	—0.038	1.490	0.808	2.298	2.276	—0.022	10.1	4.8	6.1	+ 5
9	4/ 4/38	.....	0.390	1.099	1.489	1.588	—0.099	1.679	0.603	2.282	2.235	—0.047	11.3	5.0	8.0	+ 4
10	4/ 7/38	.....	0.396	1.185	1.581	1.588	0.007	1.868	0.712	2.580	2.235	—0.345	10.3	4.5	5.9	+ 3
11	4/10/38	.....	0.293	1.236	1.529	1.588	0.059	1.537	0.706	2.243	2.235	—0.008	9.7	4.2	6.1	— 8
12	4/13/38	.....	0.371	1.272	1.643	1.588	—0.055	2.332	0.720	3.052	2.235	—0.817	10.0	3.7	7.0	— 3
Average for entire period.....			0.362	1.198	1.560	1.588	0.028	1.854	0.685	2.539	2.235	—0.304	10.3	4.3	6.7	— 1

* Patient E. M., a man aged 28. The diet supplied 2,040 calories and 58 Gm. of protein. The changes in the calcium and the phosphorus balance following a high vitamin D intake are essentially the same as those reported for patient M. C. (table 1). There was a slight rise in serum calcium, with a fall in phosphatase activity, following the high intake of vitamin D.

The average for the 4 patients varied from 9.6 to 10.1 mg. per hundred cubic centimeters, which is normal. The inorganic serum phosphorus showed considerable variation, averaging from 3.5 to 4.8 mg. per hundred cubic centimeters. These values are within the limits of normal.

In the 2 patients with atrophic spondylitis the phosphatase activity was rather constant. The average of four determinations was 8.4 King

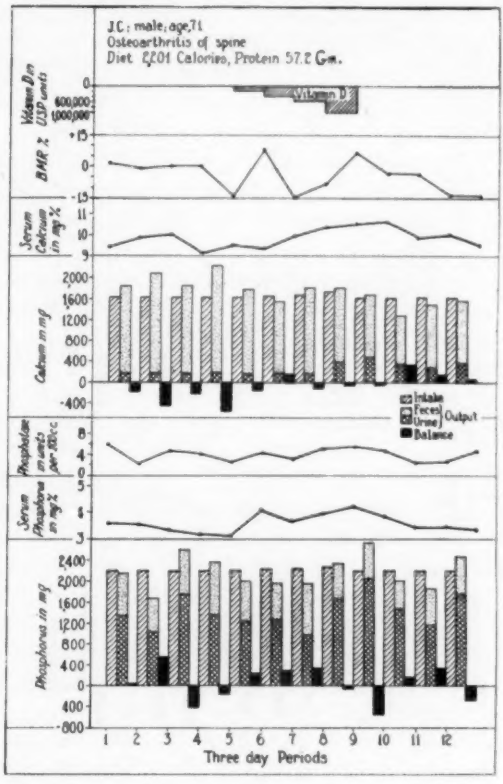


Fig. 1 (case 3, J. C.).—The increased urinary excretion, decreased fecal excretion and diminished negative balance of calcium and phosphorus following the administration of massive doses of vitamin D. There is also a slight increase in serum calcium, serum inorganic phosphorus and phosphatase activity during the period of high vitamin D intake.

units per hundred cubic centimeters of serum in E. M. (table 2) and 8.1 King units per hundred cubic centimeters in A. G. (fig. 2). J. C. (fig. 1) had the lowest values, with an average of 4.1 King units per hundred cubic centimeters. This is normal for a patient of this age

group. In our laboratory the lowest values have occurred in patients past the age of 60, in whom the phosphatase activity ranges from 2.0 to 7.0 King units per hundred cubic centimeters. The highest phosphatase activity occurred in M. C. (table 1), averaging 9.1 units in four determinations. This is above the normal values for patients of this age. In our series of over three hundred determinations the average for

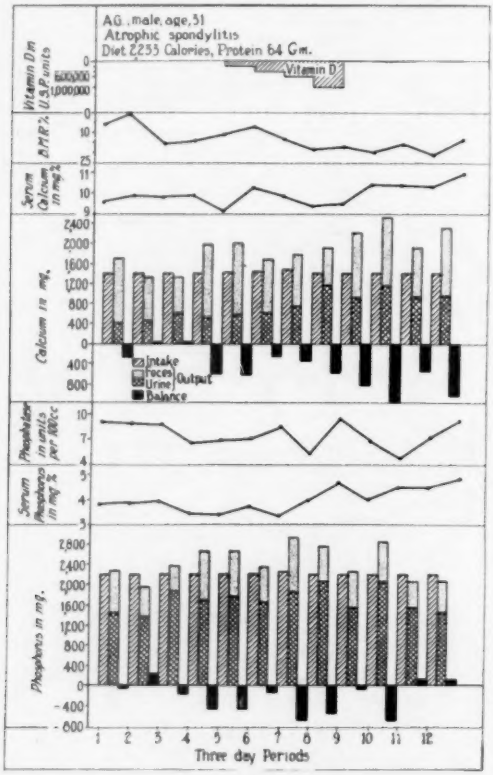


Fig. 2 (case 4, A. G.).—Note how this patient's response to high vitamin D intake differs from that of J. C. (fig. 1). There is a marked increase in the urinary excretion both of calcium and of phosphorus, with a resultant greater negative balance of each. The serum calcium and the serum inorganic phosphorus are both increased. The basal metabolic rate shows a gradual fall.

normal adults is 6.3 units, with a gradual fall in patients past middle life. In patients with obstructive jaundice the average phosphatase activity is increased to approximately 20 units and in patients with osteitis deformans the unitage was 50 to 130 per hundred cubic centimeters of

serum depending on the degree of involvement. M. C. had complained of vague pain in the right upper quadrant of the abdomen, a symptom suggestive of disease of the gallbladder. The icteric index was normal. The bromsulphalein test showed normal hepatic function. An intravenous cholecystogram revealed a normal gallbladder. We are otherwise unable to explain the increased phosphatase activity in this patient.

The basal metabolic rates of the 4 patients ranged from —15 to +21 per cent. There was great variation in the individual determinations, and the average for each patient ranged between +9 and —9 per cent during the control period. The third and the fourth determination made during the control period was lower.

Period of Administration of Vitamin D.—During four three day periods vitamin D was given, beginning with a dose of 200,000 U. S. P. units per day. This was increased by 200,000 units during each of the two succeeding three day periods (figs. 1 and 2). During the last period each patient received 1,000,000 units per day. None of the patients showed signs of toxicity; there were no gastrointestinal disturbances. There was no great change in the symptoms during the earlier part of this period. The patients still required analgesics for the relief of pain. During the last three days there ensued an increase in appetite, and the 2 patients with atrophic spondylitis had less discomfort. There was neither loss of weight nor marked change in the clinical picture. The blood pressure remained normal. There was no change in the amount of urine excreted daily.

The changes produced in the metabolism of calcium and phosphorus were striking (tables 1 and 2, figs. 1 and 2). Three patients showed a decrease in the negative balance, while A. G. (fig. 2) increased the total excretion both of calcium and of phosphorus in the feces and in the urine, as compared with excretion during the control period.

In all 4 patients there was a marked increase in the urinary excretion of calcium (tables 1 and 2, figs. 1 and 2), which reached its highest concentration during the last three days, when the intake of vitamin D was 1,000,000 units per day. The concentration of urinary calcium was increased from 40 to 120 per cent. The urinary excretion of calcium by A. G. (fig. 2) was 1.165 Gm., which approximated the total amount ingested in food. In 3 patients the excretion of calcium in the feces was decreased from 310 to 335 mg. less than during the control period. In A. G. the fecal excretion of calcium was slightly increased. With the high urinary excretion of calcium there resulted the marked negative calcium balance observed in this patient.

There was a shift in the negative balance of phosphorus toward the positive side in 3 patients, mainly because of a decrease in the fecal excretion of phosphorus. The urinary excretion of phosphorus was diminished in J. C. and E. M., while in M. C. it showed a small increase.

In A. G., however, both the urinary and the fecal excretion of phosphorus was increased, producing a negative balance of 0.446 Gm., as compared with the negative balance of 0.116 Gm. during the control period.

There was no appreciable change in the average level of serum calcium during the entire period of administration of vitamin D. In 2 patients it rose slightly during the last three day period; in M. C. it showed no change, and in A. G. there was a definite fall in the serum calcium. The serum inorganic phosphorus was increased during the last three day period in all 4 patients.

The serum phosphatase activity showed great variation in all 4 patients. The average activity was decreased in 3 patients and increased in 1, M. C. (table 1). We are unable to explain this high phosphatase rise. The highest value, 15.5 King units per hundred cubic centimeters, was increased by more than 100 per cent over the normal. The basal metabolic rates were lower than average during this period. The fall, however, was not progressive with the increasing doses of vitamin D.

Period Following Administration of Vitamin D.—During the last twelve days of investigation the patients did not receive any medication with vitamin D. Slight subjective improvement ensued in the 2 patients with atrophic spondylitis. In J. C. the attacks of acute pain in the shoulders and arms were less severe and occurred less frequently. There was no change in the condition of M. C., and analgesics were continued for the relief of severe pain. There was an increase in the appetites of all 4 patients.

The metabolic effect of vitamin D continued through this period (tables 1 and 2 and figs. 1 and 2). In J. C. the positive calcium balance, 0.112 Gm. per three day period, continued, while in E. M. it was 0.028 Gm. M. C. remained in negative balance; however, this decreased from 0.558 Gm. during the control period to 0.486 Gm. In A. G. there was a further increase in the negative balance, with a loss of 0.833 Gm. of calcium per three day period.

The maximum rise in the urinary concentration of calcium occurred during this period, averaging 13.2 mg. per hundred cubic centimeters for all 4 patients, as compared with 4.8 mg. per hundred cubic centimeters during the control period. The fecal excretion of calcium was low in 3 patients, while in A. G. it was increased as compared with the control period. The average level of serum calcium was higher in 3 patients during this period. The highest occurred in E. M. and was 11.3 mg. per hundred cubic centimeters. There was no increase in the serum calcium in M. C.

The phosphorus balance remained approximately the same as during the control period. There was a slight increase in the urinary excretion of phosphorus but a corresponding decrease in the fecal loss. M. C.

showed an increase in the retention of phosphorus, with a positive balance of 0.092 Gm. per three day period. The other 3 patients remained in negative balance. The average level of serum inorganic phosphorus was increased in 2 patients. In E. M. it was lower, while in J. C. it showed no change.

There was no appreciable change in phosphatase activity, the average values being lower than those observed during the control period, except in the case of M. C., in whom it remained at a high level.

The basal metabolic rates averaged lower in 3 patients and were slightly elevated in J. C. There was no loss of weight or change in pulse rate or blood pressure.

COMMENT

Observations made during the control period confirm the assertion of Ropes and associates [9] that there is no primary disturbance of calcium and phosphorus metabolism in patients with degenerative arthritis. We do not know of any metabolic studies on patients with atrophic spondylitis. Golding [18] reported that the serum calcium of patients with this condition was at a high normal level. The 2 patients whose cases we have presented did not show any abnormality in calcium and phosphorus metabolism. The calcium level, the phosphorus level and the phosphatase activity of the serum were essentially normal, as was the urinary excretion of calcium. These circumstances would appear to rule out parathyroid dysfunction both in degenerative arthritis of the spine and in atrophic spondylitis.

Nicolaysen [19] has shown that vitamin D increases the absorption of calcium from the intestinal tract of rats. He reported that the slightly increased absorption of phosphorus is due to this increased absorption of calcium. We conclude that the decreased fecal excretion of calcium in 3 patients during the period of high vitamin D intake and in the subsequent period is due to the increased absorption of calcium from the intestinal tract. This increased absorption was rather constant in 3 patients and averaged 0.284 to 0.335 Gm. per period. However, there was an increased loss of calcium in the urine, this factor appearing to be responsible for maintaining the serum calcium at the normal level.

So far as we are aware, there is not as yet any accurate quantitative clinical measurement of the circulating parathyroid hormone. In patients

18. Golding, F. C.: Spondylitis Ankylopoietica, Brit. J. Surg. **23**:484 (Jan) 1936.

19. Nicolaysen, R.: Studies upon the Mode of Action of Vitamin D: II. The Influence of Vitamin D on the Fecal Output of Endogenous Calcium and Phosphorus in the Rat, Biochem. J. **31**:107 (Jan.) 1937; III. The Influence of Vitamin D on the Absorption of Calcium and Phosphorus in the Rat, ibid. **31**:122 (Jan.) 1937.

without primary disturbance of the calcium and phosphorus metabolism (and with normally functioning liver and kidneys) an alteration in the activity of the parathyroid glands may be reflected in the phosphatase activity of the serum. With an associate we [20] have observed low phosphatase activity in the serum of a patient with chronic hypoparathyroidism. This was corrected, and the activity remained at higher normal levels after a successful transplanting of parathyroid tissue culture, as shown by subsequent clinical and metabolic studies.[20] Hanson and associates [21] and also Albright and Sulkowitsch [8] observed a decrease in the serum phosphatase after administration of massive doses of vitamin D. In 3 of our patients there was a slight fall in the serum phosphatase activity.

It is difficult to explain the different response of A. G. to large doses of vitamin D. During the control period he had the highest average urinary excretion of calcium. On the administration of vitamin D the percentage increase in the concentration of the urinary calcium was approximately the same as the average of the other 3 patients; however, the total urinary output of calcium rose to a much higher level. It was 1.163 Gm. per three day period at its maximum excretion. This was almost as high as his calcium intake. With the slight increase in fecal excretion of calcium this resulted in a negative balance of — 1.102 Gm. for one period. He also differed from the other 3 patients in that the urinary excretion of phosphorus was greatly increased during the twelve days of high vitamin D intake. Albright has suggested that vitamin D may exert an influence on the excretion of phosphorus similar to that of the parathyroid hormone, causing the skeletal demineralization encountered in certain cases of hypervitaminosis D. Such an effect was undesirable in the case of A. G., who had generalized bone atrophy, as shown by roentgen examination.

Vitamin D as administered in this investigation did not produce any demonstrable changes in the activity of the thyroid. The basal metabolic rate dropped slightly. However, this drop was similar to that observed in normal persons subjected to repeated determinations of the basal metabolic rate. It was apparently due to training and the better cooperation of the patients during the latter part of the investigation.

There was an increase in the appetite of all 4 patients during and also after the administration of high vitamin D. This suggests an increased activity of the thyroid. However, there was no change in

20. Houghton, B. C.; Klassen, K. P., and Curtis, G. M.: Studies in Human Parathyroid Transplantation, Ohio State M. J. **35**:505 (May) 1939.

21. Hanson, A. E.; McQuarrie, I., and Ziegler, M. R.: Effects of Parathyroid and of Vitamin D on Blood Phosphatase, Calcium and Phosphorus in Osteogenesis Imperfecta, Endocrinology **22**:1 (Jan) 1938.

body weight, pulse rate or blood pressure. The excretion of iodine in the urine, as revealed by urinalyses for iodine, was not increased in these patients. Curtis and Puppel [22] have demonstrated an increased loss of iodine in the urine in the majority of patients with untreated hyperthyroidism. Our patients were all maintained on a constant, controlled, low iodine diet. It would appear that increased function of the thyroid would have been reflected in an increased excretion of iodine in the urine.

Reed and his associates [23] observed an increase in the metabolic rate of dogs and of rats after the administration of subtoxic doses of vitamin D. Since no such results were obtained in thyroparathyroidectomized dogs,[24] these investigators concluded that vitamin D produced its calorigenic effect through the thyroid. We did not obtain any evidence in this investigation to support their conclusions.

Certain data suggest that the beneficial results of the administration of large doses of vitamin D are due to the resultant increased concentration of the serum calcium. Thus, Brunschwig [25] has shown that the injection of calcium gluconate intravenously diminishes the pain in patients with metastatic carcinoma of the skeleton.

We observed that the subjective improvement of 3 patients coincided with the rise in the serum calcium, while the fourth, M. C. (table 1), who had no such rise, did not notice any change in her symptoms. The slight increase in motion of the hips in 2 patients might be explained on the basis of decreased pain. Roentgenograms did not reveal corresponding changes in the appearance of the articular surfaces or spaces.

Hubbart [26] in reviewing the literature on hypervitaminosis D warned against the indiscriminate use of vitamin D in the treatment of patients. Vitamin D given in toxic doses is said to produce cell degeneration and calcification. Determining factors are the possible sensitivity of certain patients to this vitamin, the dose administered, the duration of treatment and the calcium, possibly also the phosphorus, intake. The elevation of the serum calcium was but small in our patients, yet the urinary excretion of calcium was increased far above the normal physiologic level. In the presence of renal damage, infection or alkaline reaction of the urine

22. Curtis, G. M., and Puppel, I. D.: Increased Urinary Iodine of Hyperthyroidism, Arch. Int. Med. **60**:498 (Sept.) 1937.

23. Reed, C. I.; Thacker, E. A; Dillman, L. M., and Welch, J. W.: The Effect of Irradiated Ergosterol on the Metabolism of Normal Dogs, J. Nutrition **6**:355 (July) 1933. Reed, C. I.: Effect of Heavy Administration of Viosterol on Metabolism of Rat, Proc. Soc. Exper. Biol. & Med. **32**:274 (Nov.) 1934.

24. Deutsch, H.; Reed, C. I., and Struck, H. C.: The Role of Thyroid in the Calorigenic Action of Vitamin D, Am. J. Physiol. **117**:1 (Sept.) 1936.

25. Brunschwig, A.: Observations on the Administration of Large Doses of Calcium in Metastatic Carcinoma in Bone, Am. J. Cancer **25**:721 (Dec.) 1935.

26. Hubbart, A. W.: Hypervitaminosis D, Illinois M. J. **72**:253 (Sept.) 1937.

deposition of calcium in tubules or calices certainly might occur. The concentration of the urinary calcium in 1 of our patients was as high as is encountered in patients with hyperparathyroidism.

The number of patients is too small to draw any conclusions as to the efficacy of vitamin D in the treatment of chronic arthritis. There are in the literature, however, reports covering large series of cases.[27] We agree with Irons [1] and Hubbart [26] that vitamin D in massive doses should be used with caution and only in patients who are under close observation and are followed by frequent laboratory examination not only of the serum calcium but of the concentration of calcium element in the urine.

SUMMARY

Complete studies of calcium and phosphorus metabolism were made on 2 patients with atrophic spondylitis and 2 patients with degenerative arthritis of the spine before, during and subsequent to the administration of massive doses of vitamin D.[15]

There was no primary disturbance in the calcium and phosphorus metabolism in the patients with atrophic spondylitis or with degenerative arthritis of the spine.

The administration of massive doses of vitamin D resulted in an increased retention of calcium in 3 patients, while the negative calcium balance of 1 was increased. The urinary excretion of calcium was increased for all 4 patients. The fecal loss of calcium of 3 patients was decreased, and that of 1 was increased. Three patients had a slight rise in the concentration of serum calcium.

Subsequent to the administration of vitamin D a slight increase in phosphorus retention ensued in 3 patients, while 1 showed an increase in the loss of phosphorus. The urinary excretion of phosphorus was increased for all 4 patients, while the fecal excretion of 3 was diminished and that of 1 was slightly increased. The serum inorganic phosphorus was elevated in 3 patients. The phosphate activity of the serum was slightly decreased in 3 patients.

Vitamin D in massive doses as administered in this investigation did not produce demonstrable changes in the activity of the parathyroids or the thyroid.

Kinsman Hall, Ohio State University College of Medicine.

Ohio State University College of Medicine.

27. Hench, P. S.; Bauer, W.; Fletcher, A. A.; Christ, D.; Hall, F., and White, T. P.: The Problem of Rheumatism and Arthritis: Review of American and English Literature for 1935 (Third Rheumatism Review), Ann. Int. Med. **10**:754 (Dec.) 1936. Hench, P. S.; Bauer, W.; Christ, D.; Hall, F.; Holbrook, W. P.; Key, J. A., and Slocumb, C. H.: The Present Status of Rheumatism and Arthritis: Review of American and English Literature for 1936 (Fourth Rheumatism Review), ibid. **11**:1089 (Jan.) 1938.

TOXICITY OF PYRIDINE IN MAN

LEWIS J. POLLOCK, M.D.

ISIDORE FINKELMAN, M.D.
AND
ALEX J. ARIEFF, M.D.
CHICAGO

Although pyridine is used in many laboratories and chemical industries as a solvent for anhydrous mineral salts, in synthesis of organic compounds and in analytic procedures, only a few instances of its toxic effect on man have been recorded.

The unfortunate outcome of an experiment in the treatment of epilepsy by the use of pyridine afforded us an opportunity to observe the development of its toxic effect. Since the effect of pyridine on the human organism has been incompletely studied and knowledge concerning its action is sketchy, we concluded that our observations were worthy of description.

In searching for an anticonvulsant which does not produce a narcotic side effect, we studied the effect of pyridine on convulsions produced by the intravenous injection into rabbits of minimal convulsant doses of metrazol.

It was found that pyridine and some of its derivatives, such as niacin (nicotinic acid) amide, significantly reduced the severity of the convulsions and in many cases prevented any motor disturbance of any nature.[1] Since pyridine had been used safely some years ago for the treatment of asthma, chiefly by inhalation but also by oral administration in doses of 6 to 25 minims (0.37 to 1.54 cc.),[2] we decided to study the effect of the administration of 10 minims (0.61 cc.) three or four times a day for a month on 5 patients suffering from epilepsy.

We propose to describe the seemingly innocuous action observed during this month and report 2 cases in which there were later severe effects, in 1 case producing death.

Pyridine was discovered in Dippel's animal oil by Anderson (1851) and later found in coal tar and as a constituent of numerous alkaloids. It is also formed during roasting of coffee. It is a colorless liquid of

From the Department of Nervous and Mental Diseases, Northwestern University Medical School, and the Minnie Frances Kleman Memorial Fund.

1. Pollock, L. J., and Finkelman, I.: J. Nerv. & Ment. Dis. **96**:424, 1942.

2. Bartholow, R.: A Practical Treatise on Materia Medica and Therapeutics, New York, D. Appleton and Company, 1890, p. 386.

characteristic odor; it is miscible with water and with alcohol and boils at 115 C.

The fate of pyridine in organisms was first studied by His [3] (1887), who found that in dogs it is excreted as methylpyridyl ammonium hydroxide.

For the most part the studies on its effects on living organisms have been conducted on frogs. Brunton and Tunnicliffe [4] claim that the depressant effect on the nervous system of frogs is mainly confined to the sensory system, mostly in the spinal cord and that large doses depress the respiratory center. In frogs large doses produce convulsions. Although large doses paralyze cardiac muscle, ordinary ones do not depress the heart, and with systemic administration Brunton and Tunnicliffe said, "The heart was the last organ to die." In man pyridine is said to increase the power of the cardiac contraction and raise the tension.[5]

As to its toxicity, von Oettingen [6] stated that it is not marked. Distler [7] reported that in rabbits orally administered doses of 2 Gm. per 1.5 Kg. caused only slight depression and twice this dose caused marked depression and killed the animals by paralysis of the respiratory center. The minimal fetal dose for guinea pigs was reported by Brunton and Tunnicliffe as 87 mg. per hundred grams with intraperitoneal injection and as 400 mg. per hundred grams with oral administration. His [3] administered 0.1 Gm. daily in the form of a 5 per cent solution to dogs for thirty-five days without observing any toxic symptoms aside from occasional vomiting and diarrhea.

Pyridine in the doses administered to rabbits during our study of its anticonvulsant property caused only evanescent immediate effects and these in only a few animals. Of 39 animals receiving an intravenous injection of 110 mg. of pyridine per kilogram of body weight, 3 immediately sprawled out and remained in a hypotonic, ataxic paretic state for no longer than three minutes, then entirely recovered. Sialorrhea was observed occasionally. Of 7 receiving 220 mg. per kilogram, 4 sprawled out for less than three minutes.

Single feedings of 220 to 660 mg. per kilogram, inclusive, failed to produce any effect with one exception of sprawling shortly after 220 mg. was administered. Of 12 animals receiving 880 mg. per kilogram, 1 was immobile for a time, another startled easily, 1 died four days later and

3. His, W.: Arch. f. exper. Path. u. Pharmakol. **22**:253, 1887.

4. Brunton, T. S., and Tunnicliffe, F. W.: J. Physiol. **17**:272, 1894.

5. De Renzi, E.: Riv. clin. e terap. **8**:169, 1886.

6. von Oettingen, W. F.: The Therapeutic Agents of the Pyrrole and Pyridine Group, Ann Arbor, Mich., Edwards Brothers, Inc., 1936.

7. Distler, H.: Ueber einige Wirkungen des Pyridin, Inaug. Dissert., Erlangen, Junge & Sohn, 1887.

another died two days after feeding. Of 2 animals receiving 1,320 mg. per kilogram, 1 was unable to walk for an hour and the other remained sick and weak for twenty-four hours. One animal after a feeding of 1,760 mg. per kilogram sprawled out immobile for a long time.

Feedings continued for five to seven days failed to produce any effect in 4 animals receiving 44 mg. per kilogram per day. Of 4 receiving 165 mg. per kilogram per day, 1 died on the sixth day, and of 14 receiving 220 mg. per kilogram per day, 1 died, probably because of being tube fed while the stomach was distended with food.

The immediate effects of inhalation of pyridine noted in man have included flushing of the face, quickening of the pulse and respiration, temporal headache, a full sensation of the head approaching giddiness and a desire to sleep.[8] After eight days' treatment 1 asthmatic patient experienced nausea and vertigo.[9] Lublinski [10] reported a case in which there was marked tremor of the limbs with nausea and another in which there were vomiting, dizziness and severe headache. In all cases the effects followed inhalations lasting one to one and a half hours. More serious effects were noted by Ludwig [11] when crude pyridine containing impurities of picoline, lutidine and collidine was inhaled over a considerable period by employees in two chemical works. Among the lesser symptoms observed were headache, vertigo, abdominal pain, heart burn, vomiting, disturbed sleep, weakness, giddiness, anorexia and nervousness.

There were 2 instances of serious effects. In 1 case transient paralysis of the facial nerve, periods of unconsciousness, ataxia and unequal pupils developed. Urobilinogen was excreted in the urine, and bilirubin was found in the serum in an amount of 2.15 mg. per hundred cubic centimeters.

In the second case of serious complication a 37 year old man had worked with crude pyridine off and on for two years, when headache, vertigo, nausea, anorexia and insomnia developed. Then suddenly paralysis of the right facial nerve ensued, and two days later there developed partial paralysis of the left oculomotor nerve, paralysis of the abducens nerves, partial paralysis of the palate, absence of the gag reflex and paralysis of the recurrent laryngeal nerves. There were cerebellar ataxia on the right side, thermanesthesia and slight hemiparesis of the right side. The level of urobilin was increased in the urine but was normal in the blood.

The patient's condition was interpreted by Ludwig to be the result of pseudoencephalitis of Wernicke. After three months the symptoms and signs largely disappeared.

8. Neff, J. S.: New York M. J. **43**:299, 1886.
9. See, G.: Bull. gen. de thérap. **108**:529, 1885.
10. Lublinski, W.: Deutsche med. Ztg. **2**:985, 1885.
11. Ludwig, H.: Arch. f. Gewerbepath. u. Gewerbehyg. **5**:654, 1934.

We did not find any reports of toxic effects other than heart burn and occasional nausea following the use of pyridine in the doses ordinarily prescribed by mouth, 6 to 25 minims.

However, Helme [12] reported a case in which accidental swallowing of half a cupful of commercial pyridine resulted in death in forty-three hours. After the ingestion the patient vomited five times in seven hours; when admitted to the hospital he was pale and slightly cyanosed, with a temperature of 103.4 F., a pulse rate of 128 per minute and a respiratory rate of 40 per minute. He complained of a choking sensation, precordial pain, abdominal pain and inability to swallow. Acute congestion of the lungs, bronchitis and purulent expectoration developed, and the patient became wildly delirious and died. Examination of the urine failed to reveal any abnormality, and at autopsy no changes in the heart, kidney or spleen were encountered. The liver had a few fatty patches. The chief lesions were those of the epiglottis, trachea, bronchi, lungs, esophagus and stomach.

EFFECT OF ADMINISTRATION OF PYRIDINE TO FIVE PATIENTS SUFFERING FROM EPILEPSY

Five patients suffering from epilepsy were admitted to Passavant Memorial Hospital and placed in a special ward during the period of study. Prior to the administration of pyridine the first few days to a week of hospitalization were occupied by a battery of tests devised to reflect any visceral, chemical or blood changes, and after medication with pyridine was begun, these were repeated at weekly intervals. During most of the period the patients were allowed to take their previous medication of sodium bromide, phenobarbital or dilantin sodium alone or in combination. To 2 patients pyridine was administered for ten days, to 2 others for twenty-eight days and to another for thirty days. After discharge from the hospital the fifth patient continued to take pyridine for seven days; he took none for forty days and then took it again for twenty-five days, when he became seriously ill. One who had taken it for twenty-eight days in the hospital continued for fifty additional days, without noticeable toxic effect. Administration of pyridine to the other patients was discontinued.

We did not observe any change in temperature, pulse, respiration or blood pressure during the administration of pyridine in doses of 10 minims (0.6 cc.) occasionally three times but usually four times a day. There was an increase of body weight of 1 to 6 pounds (0.5 to 3 Kg.). At one or another time there were complaints of a minor nature of anorexia, eructations, nausea, occasional vomiting, gastric distress, fulness, occasional pain or pressure in the abdomen, abdominal distention.

12. Helme, G. E.: Brit. M. J. **2**:844, 1893.

occasional headache, faintness, fatigue, weakness, mental depression and often restless sleep.

The blood picture as reflected by numerous examinations showed a tendency to a decrease in the number of leukocytes in the 5 patients from 9,000 to 6,000, from 9,500 to 6,000, from 9,500 to 5,000, from 6,000 to 5,000 and from 10,000 to 8,200, respectively. There was a tendency for an increase in the percentage of eosinophils in 3 patients, from 1 to 9, from 0 to 6 and from 8 to 12, respectively. In 1 patient there was no change and in another a decrease from 5 to 2 per cent. Occasionally, an increase of basophils was encountered. Vacuolation, ordinarily reported as being seen in the red cells of experimental animals, was noted in eosinophilic leukocytes in 2 patients; in 2 patients there was a slight increase in the number of lymphocytes. Otherwise, there was no change in the number of red cells, the concentration of hemoglobin, the coagulation time, the bleeding time or the sedimentation rate.

Little or no free hydrochloric acid was found in the stomach before treatment was begun, and no change was observed after treatment.

The feces did not show any change, and bowel movements were not increased. The urine of 1 patient, who later became violently ill and died, was normal throughout the medication with pyridine. In the urine of 3 patients erythrocytes were encountered in small numbers; in that of 2 a trace of albumin was present before treatment and did not increase, and in that of 1 for whom treatment was discontinued a few hyaline casts were found before treatment and at the end of ten days when treatment was discontinued. The results of phenolsulfonphthalein excretion tests did not show any change from normal. The amounts of calcium, sodium, potassium, chlorides, nonprotein nitrogen and urea nitrogen in the blood remained constant and within normal limits, as was the case with the carbon dioxide capacity, the result of the van den Bergh test, the icterus index and the result of the hippuric acid test of hepatic function. Results of repeated galactose tolerance tests on 4 patients showed that in 1 the total amount excreted was 6.5 Gm. before treatment was instituted and 1.8 Gm. after twenty-eight days' treatment; in the other 3 patients the amount excreted was quite below normal limits before treatment and fell from 2.8 to 1.8 Gm., from 2.38 to 1.4 Gm. and from 2.6 to 1.56 Gm., respectively.

In all of the patients before treatment the phosphatase value was at a high normal level and fell after treatment from 5.5 to 1.7 King units per hundred cubic centimeters, from 4.9 to 2.36 units, from 5.57 to 2.84 units and from 4.9 to 3.9 units, respectively, in the adults and from 8.8 to 5.1 units in a boy 16 years old.

The blood level of inorganic phosphorus was within normal limits in all 5 patients before treatment and was increased in the 4 adults from 2.76

to 3.2 mg. per hundred cubic centimeters, from 2.86 to 3.04 mg., from 2.86 to 3.16 mg. and from 2.88 to 3.49 mg., respectively, all increases being within normal limits. In the case of the boy it fell from 5.66 to 3.8 mg. per hundred cubic centimeters.

In 4 patients the blood level of cholesterol in milligrams per hundred cubic centimeters fell from 214 to 170, from 400 to 205, from 197 to 186 and from 318 to 285, respectively. In 1 patient it remained about the same, decreasing from 196 to 192 mg. per hundred cubic centimeters. The cholesterol esters in milligrams per hundred cubic centimeters were diminished in the same sequence from 141 to 121, from 298 to 128, from 127 to 125, from 239 to 203 and from 134 to 117, respectively.

There was a slight increase of serum total protein within normal limits in 4 patients from 5.6 to 6.2 Gm. per hundred cubic centimeters, from 6.4 to 7.13 Gm., from 6.2 to 6.8 Gm. and from 5.57 to 7.2 Gm., respectively, and a decrease in 1 from 7.02 to 6.9 Gm. At the same time the globulin fraction was somewhat increased in the first 4 patients in the same order from 1.06 to 1.45 Gm. per hundred cubic centimeters, from 1.6 to 2.11 Gm., from 1.1 to 1.43 Gm. and from 1.12 to 2.3 Gm., respectively, and decreased in the fifth patient from 2.22 to 1.68 Gm., all changes being within normal limits.

From this study it was concluded that there was no evidence of damage to any organ and that with the exception of some minor subjective complaints and gastrointestinal disturbances the administration of 10 minims of pyridine four times a day did not produce any toxic effect. Therefore, treatment of 2 patients was continued, and medication was started for another patient, who had not been studied in the hospital. In 2 of them conditions developed which we feel were the result of damage produced by pyridine.

REPORT OF TWO CASES

CASE 1.—*Summary.*—During medication with pyridine in doses of first 30 minims (1.85 cc.), then 40 minims (2.46 cc.), a day abdominal pain, nausea, vomiting, headache and anorexia suddenly developed in a young man suffering from a convulsive disorder. Jaundice and edema of dependent parts followed. Hiccuping accompanied the symptoms just mentioned. There was a mild fever. Azotemia and albuminuria progressed. Death ensued eight days after the onset of the acute symptoms. The condition appeared to be of hepatic and renal origin.

Detailed Report.—O. G., a white man aged 32, was first admitted to the Montgomery Ward Medical Clinics of Northwestern University Medical School on May 9, 1938. Nothing in his familial or personal history was pertinent to his illness. The first attack of a convulsive seizure occurred at the age of 15, while he was on a "high ride" in an amusement park. Attacks then were repeated with increasing frequency, so that in 1933 he was having one or more attacks daily. In addition, attacks of petit mal occurred one to three times a week. The attacks were not preceded by an aura, nor did they begin with any motor disturbance indicating a focal lesion. Neurologic examination, as well as all other examina-

TABLE 1.—*Chemical Changes in the Blood of Five Patients with Epilepsy Taking Pyridine During a Month's Experiment to Determine the Anticonvulsant Effect of This Compound*

	Date	Non-protein Nitrogen, Mg./100 Cc.	Icterus Index, Units	Cholesterol, Mg./100 Cc.	Cholesterol Esters, Mg./100 Cc.	Total Protein, Gm./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Phosphorus, Mg./100 Cc.	Calcium, Mg./100 Cc.	Chlorides, Mg./100 Cc.	Phosphatase, King Units/100 Cc.	Sodium, Mg./100 Cc.	Potassium, Mg./100 Cc.	Urea Nitrogen, Mg. of 100 Cc.	Hippuric Acid, % of Normal	Carbon Dioxide Capacity, Vol. %	van den Bergh Reaction, Indirect, Mg. of Bilirubin /100 Cc.
Patient 1	4/29	30.8	5	214	141	5.66	4.6	1.06	2.76	10.44	468	5.59	341	19.6	12.5	141.5	47.5	0.5
(case 1)	5/14	32.2	6	192	133	6.6	5.28	1.32	2.94	9.62	470	3.12	336	21	12.5	130.5	60	0.5
	5/21	22.6	7	179	119	7	5.33	1.67	3.12	10.05	472	2.99	348	21	12.2	126	54.7	1.56
	5/27	31.2	7	170	121	6.25	4.8	1.45	3.2	9.7	460	1.7	345	24.4	11.3	133	54.2	0.85
Patient 2	5/ 1	37	7	400	280	6.44	4.84	1.6	2.86	10.48	464	4.9	342	29.6	11.7	160	48	0.5
	5/14	35	7	295	206	6.93	5.25	1.68	4	10.05	454	3.74	342	21.3	13.2	129	47.3	0.5
	5/21	25.4	7	277	177	7.04	5.39	1.65	3.8	10.28	470	2.4	347	21	10.9	133	50.5	0.5
	5/27	28.9	6	205	128	7.13	5.02	2.11	3.04	10.2	455	2.36	347	23.2	8.7	132	53.1	0.5
Patient 3	4/29	31.1	7	197	127	6.25	5.15	1.1	2.86	10.82	424	5.57	334	22.1	15.4	125	54.8	0.85
	5/14	27.8	7	229	142	7.2	5.44	1.76	3.41	10.7	470	3.34	335	20.8	9.15	136	54.6	0.5
	5/21	24.2	6	200	123	7.5	5.26	2.25	3.62	10.8	470	2.74	347	22.3	10.9	113	51.5	0.5
	5/27	30.6	6	186	125	6.87	5.44	1.43	3.16	9.75	475	2.84	338	20.8	9.8	136	54	0.5
Patient 4	5/20	21.6	5	196	134	7.02	4.8	2.22	5.66	10.62	450	8.84	342	23.2	11.1	104	56.8	0.5
	5/27	30.1	5	192	117.8	6.91	5.23	1.68	3.8	10.2	475	5.1	337	19.8	9.6	126	53.1	0.5
Patient 5	4/29	38.8	7	318	239	5.57	4.45	1.12	2.88	10.82	452	4.92	336	21.9	17.8	125	56.8	0.5
	5/14	29.2	7	285	203	7.2	4.9	2.3	3.49	10	450	3.9	348	21.9	11.7	110	51.9	0.85

tions, failed to reveal any abnormality. Although during administration of sodium bromide attacks of grand mal had been stopped for six months at one time, they recurred and were then, as were the attacks of petit mal, recalcitrant to treatment by bromides, phenobarbital and dilantin sodium.

On April 29, 1940, the patient was admitted to the Passavant Memorial Hospital. For twelve days he was given 30 minims (1.85 cc.) of pyridine a day and for an additional eighteen days 40 minims (2.46 cc.) a day. No significant changes in bodily function indicative of any toxic effect were noted.

After his discharge from the hospital on June 14 he was again placed on a treatment schedule of 10 minims of pyridine three times a day and 1½ grains (0.09 Gm.) of phenobarbital four times a day. On June 21 his supply of pyridine was exhausted, and since he had suffered from acute pharyngitis, no more pyridine was prescribed. Three days later, after taking magnesium sulfate, the patient experienced a pain in the lower part of the abdomen. He was admitted to the Cook County Hospital on June 25. His condition was given the diagnosis of diverticulitis; within a few days the symptoms subsided, and he was discharged on June 29.

On July 29 he was again placed on a treatment schedule of 10 minims of pyridine three times a day and 1½ grains of phenobarbital four times a day. On August 20 he was awakened from sleep by a sharp pain in the right side of the abdomen. He vomited soon after, then felt chilly and feverish. A headache of a dull nature was noted. The next day the abdominal pain, headache and vomiting continued. Diminished urinary output was noted, only a small amount of dark urine having been passed on the second day of illness. On the third day, the symptoms continued and hiccuping developed. During these three days he had had only one bowel movement, with a watery stool. On the third day he was admitted to the Cook County Hospital. The temperature was 101 F., the pulse rate 120 per minute, the respiratory rate 24 per minute and the blood pressure 110 systolic and 60 diastolic. The patient's tongue was coated and his breath foul; he hiccuped frequently and occasionally vomited. There was dulness in the middle lobe of the right lung, and rales were heard over this area. Roentgenograms of the chest showed the diaphragm was elevated on the right side. A specimen of urine obtained by catheterization contained albumin (4 plus) but neither blood nor bile. On August 23 examination of the blood showed that per hundred cubic centimeters it contained 89 mg. of nonprotein nitrogen, 13 mg. of uric acid, 104.6 mg. of urea, 7.5 mg. of creatinine, 3.37 Gm. of albumin, 1.58 Gm. of globulin, 131 mg. of cholesterol, a trace of cholesterol esters, 5.15 mg. of phosphorus, 6.55 King units of phosphatase and 400 mg. of chlorides. Slight secondary anemia and leukocytosis (17,100 cells) were present. Per hundred cubic centimeters the urine contained 100 mg. of urea, 13.7 mg. of ammonia nitrogen and 24 units of diastase.[12a] Albumin (4 plus) was present in the urine, and urea clearance was 9 cc. in one hundred and sixty-one minutes.

On August 24 the patient appeared worse. His scleras and skin were icteric. There was marked tenderness in the abdomen, and hepatic dulness seemed increased. A Levine tube was introduced, and solutions of dextrose and sodium chloride were given intravenously. On August 25 his temperature was 99.6 F. and his blood pressure was 108 systolic and 60 diastolic. He appeared acutely ill. Subconjunctival hemorrhages appeared in the left eye. Edema of the eyelids and the

12a. The unit of diastase used is the one commonly employed in the United States. One unit represents the quantity of urine in cubic centimeters that will convert a 0.1 per cent starch solution to sugar in half an hour at 37 C. Normal is 8 to 32.

dorsa of the feet appeared. Respiration was difficult, and moist rales were heard over the bases of the lungs. On August 26, the blood contained 116 mg. of nonprotein nitrogen per hundred cubic centimeters and the icterus index was 50; the urine continued to contain large quantities of albumin. On August 27 as the jaundice increased the patient became more drowsy and vomited more frequently; the vomitus contained blood (4 plus) as indicated by the result of the benzidine test. Edema of the face increased; the patient became irrational at times; the abdomen was tympanitic, and respirations increased to 38 per minute. Diuresis was not brought about by administration of theophylline with ethylenediamine. On August 28 the patient was in a deep stupor. The subconjunctival hemorrhages were increased, and generalized edema was present. On chemical examination the blood per hundred cubic centimeters contained 175 mg. of nonprotein nitrogen, 125 mg. of cholesterol, 20 mg. of cholesterol esters, 4.77 Gm. of albumin, 1.94 Gm. of globulin, 106 mg. of urea, 6.57 mg. of phosphorus and 6.33 King units of phosphatase. The icterus index was 28. The urine per hundred cubic centimeters contained 164 mg. of urea and 21 mg. of ammonia nitrogen. It contained albumin (4 plus) but no casts. The nitrogen urea clearance was 13 cc. in one hundred and twenty-three minutes.

On August 28, in spite of intravenous injection of fluid and administration of theophylline with ethylene diamine, prostigmine methylsulfate, oxygen and stimulants, the patient died. Permission for autopsy was refused.

CASE 2.—*Summary.*—After eleven days of administration of pyridine in doses of 30 minims per day stupor developed in a young man aged 35 suffering from a convulsive disorder due to an astrocytoma successfully treated by removal and roentgen therapy. Evidence of hepatic involvement and renal insufficiency was discovered, and during the period of illness residual focal signs of brain disease increased and aphasia and agnosia developed. After a month of severe illness the patient began to improve, and he recovered completely from the hepatic involvement and renal insufficiency and the temporary increase of cerebral disability.

Detailed Report.—W. K., a white man aged 35, was admitted to the Montgomery Ward Medical Clinics of the Northwestern University Medical School in November 1936. He had had his first convulsive seizure at the age of 31. Seizures had continued in the form of four to five attacks of petit mal daily and one to three attacks of grand mal monthly. An aura of premonition preceded these attacks. Four years later right hemiparesis and right homonymous hemianopia had developed, and the patient was operated on by Dr. Howard Naffziger. An astrocytoma of the left parieto-occipital lobe was removed, and removal was followed by roentgen therapy. The patient had continued to have convulsive seizures, but few residual signs of an organic lesion remained, namely, slight right hemiparesis with incomplete right homonymous hemianopia. Despite therapy with bromides, phenobarbital and dilantin sodium, the attacks had continued, although they were markedly diminished.

On Aug. 2, 1940 the patient was placed on a treatment schedule of 10 minims of pyridine three times a day with 1½ grains of phenobarbital four times a day. On August 12 he reported a little nausea after taking the pyridine. On August 16 his aunt reported that he had become increasingly stuporous during the preceding three days. He was sent to the Cook County Hospital that day.

On examination the patient was somewhat stuporous and appeared rather indifferent but cooperative and oriented. The temperature was 98 F., the respiratory rate 20 per minute and the blood pressure 110 systolic and 70 diastolic. The pupils were unequal, the right one being smaller than the left one, but both reacted well to light directly and consensually and in accommodation. There was a fine

TABLE 2.—*Chemical Changes in the Blood of Two Patients Taking Pyridine as an Anticonvulsant* *

	Date	Non-protein Nitrogen, Mg./100 Cc.	Uric Acid, Mg./100 Cc.	Total Protein, Gm./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Creatinine, Mg./100 Cc.	Urea Nitrogen, Mg./100 Cc.	Cholesterol, Mg./100 Cc.	Cholesterol Esters, Mg./100 Cc.	Phosphorus, Mg./100 Cc.	Phosphatase, King Units/100 Cc.	Calcium, Mg./100 Cc.	Chlorides, Mg./100 Cc.	Icterus Index, Units
Patient O. G. (case 1)															
One month's observation in hospital	4/29	30.8	....	5.66	4.6	1.06	....	12.5	214	141	2.76	5.59	10.44	466	5
	5/14	32.2	....	6.6	5.28	1.32	....	12.5	192	133	2.94	3.12	9.62	470	6
	5/21	22.6	....	7.0	5.33	1.67	....	12.2	179	119	3.12	2.99	10.05	472	7
	5/27	31.2	....	6.25	4.8	1.45	....	11.3	170	121	3.2	1.7	9.7	460	7
Period of illness	8/23	80	13	4.95	3.37	1.58	7.5	104.6	131	Trace	5.15	6.55	....	400	..
	8/26	116	....	....	....	....	....	....	...	...	....	....	....	...	50
	8/28	175	....	6.71	4.77	1.94	....	106	125	30	6.57	6.33	....	...	28
Patient W. K. (case 2)															
Period of illness	8/17	139	8.5	....	....	....	....	....	...	...	....	....	....	...	..
	8/22	137	....	....	....	....	....	....	...	...	....	....	....	...	..
	8/23	170	9.7	5.85	4.3	1.55	13	....	165	...	....	....	....	...	11
	8/26	170	....	....	....	....	....	....	...	...	....	....	....	...	..
	9/ 7	155	4.7	....	....	....	5.4	....	166	46	....	....	....	...	..
	9/18	41	....	5.98	....	....	....	....	178	120	3.33	....	9.6	...	15
	9/22	32	2.3	....	....	....	2	....	...	...	....	....	....	...	..

* One patient continued taking pyridine after he was observed for a month in the hospital while taking this drug. The other patient had not taken pyridine under observation previously.

horizontal nystagmus. The patient's speech was slow and slurred, and his responses were slow. All deep reflexes were brisk bilaterally, and superficial abdominal and cremasteric reflexes were normal. No pathologic reflexes were elicited. Examination of the fundi revealed a questionable blurring of both optic disks. Gross tests of the visual fields revealed right homonymous hemianopia. Examination of the spinal fluid revealed a clear but xanthochromic fluid under normal pressure, containing 4 cells per cubic millimeter; per hundred cubic centimeters it contained 57 mg. of total protein, 75 mg. of sugar and 680 mg. of chlorides. The urine showed albumin (4 plus) and 10 to 20 white blood cells per low power field; no casts were observed. The blood per hundred cubic centimeters contained 8.5 mg. of uric acid and 139 mg. of nonprotein nitrogen. On August 20 there was a weakness in the right lower extremity; the deep reflexes of this extremity were greater than those of the left one. The right side of the face moved with less facility than the left side. Movements of the right upper extremity were clumsy. There was considerable stupor. On August 22 the blood level of nonprotein nitrogen was 137 mg. per hundred cubic centimeters, and there was marked albuminuria. On August 23, the icterus index was 11 and the blood per hundred cubic centimeters contained 9.7 mg. of uric acid, 13 mg. of creatinine, 5.85 Gm. of total protein, 4.3 Gm. of albumin, 1.55 Gm. of globulin, 165 mg. of cholesterol and 170 mg. of nonprotein nitrogen. On August 27 there were present anomia, ataxia, acalculia, defect in body scheme, confusion and disorientation. The patient's tongue was heavily coated and his breath urinous. It became necessary to restrain him in bed. On August 30 he had epileptiform seizures, occasionally right sided, at other times generalized. From day to day he seemed to become worse; the confusion increased, and he refused to eat or to talk with visitors and became belligerent and excited. On September 7 the blood per hundred cubic centimeters contained 155 mg. of nonprotein nitrogen, 4.7 mg. of uric acid, 5.4 mg. of creatinine, 166 mg. of cholesterol and 46 mg. of cholesterol esters. A blood transfusion was performed on September 10. Two days later the patient began to show signs of recovery, and a week later he was able to converse intelligently. On September 18, the icterus index was 15 and the blood per hundred cubic centimeters contained 41 mg. of nonprotein nitrogen, 5.98 Gm. of total protein, 3.33 mg. of phosphorus, 9.6 mg. of calcium, 178 mg. of cholesterol and 120 mg. of cholesterol esters. On September 22 these blood levels had further decreased per hundred cubic centimeters to 32 mg. of nonprotein nitrogen, 2.3 mg. of uric acid and 2 mg. of creatinine, and the blood contained 1.1 mg. of phenol per hundred cubic centimeters (table 2). On October 2 a nonspecific suppurative epididymitis developed, which was treated surgically, and the patient was discharged on December 5. At this time chemical examination of the blood did not reveal anything abnormal, and the general paralysis, agnosia and other focal signs had receded to the state existing prior to the development of the acute disease.

COMMENT

The outstanding symptoms in case 1 were rapid development of uremic symptoms, anuria, subconjunctival hemorrhages, edema, jaundice and delirium. There was evidence of rapid, progressive parenchymal destruction of the liver, as shown by a marked depression of total serum protein and its fractions and a lowering of cholesterol with almost total disappearance of the ester fraction. Primary nephritis or nephrotic syndrome is excluded by these changes occurring in a brief period and

without phosphorus retention, elevation of the blood pressure or activity of the urinary sediment.

In the second case the retention of nitrogen and uric acid without elevation of phosphorus was outstanding. An inactive sediment in urine of a low specific gravity containing albumin (4 plus) speaks for an altered function of the tubules. Again a low blood level of cholesterol and generally reduced serum protein and its fractions suggest sharp depression of the function of the liver. Altered hepatic function may explain the high blood level of uric acid and the albuminuria, such as are encountered in the hepatorenal syndrome. In their discussion of the hepatorenal syndrome Orr and Helwig [13] concluded:

> There exists a close relationship between the liver and kidneys in disease since they are phylogenetically and functionally closely related. It is very probable that when the liver function breaks down in its detoxification or neutralization function that the kidneys take over the function of eliminating toxic products by excretion.

In our cases pyridine seemed to cause parenchymal damage to the liver, thus imposing on the kidneys an extra burden of eliminating toxic products in general, as well as eliminating the pyridine itself.

It has often been observed by us that when a convulsive disorder in a patient is the result of organic brain disease, such focal signs as may be evident are always increased markedly when the patient because of bromism suffers from a temporary encephalopathy. We attribute the increase of focal signs in the case reported in which there were residual signs of an astrocytoma of the brain to such a toxic encephalopathy.

CONCLUSIONS

Despite the relatively low toxicity of pyridine in animals, failure to find reports of toxic effects in man resulting from its administration in repeated doses of 5 to 25 minims (0.31 to 1.54 cc.) and absence of any evidence of toxicity in man, when careful studies were made on 5 subjects receiving 30 to 40 minims (1.85 to 2.46 cc.) of pyridine a day for periods up to a month 2 instances of later marked toxic effects were noted. In both instances the effects were those of hepatorenal disease, in 1 case leading to death, in the other case followed by recovery.

Pyridine may be added to the list of chemical poisons which may produce the hepatorenal syndrome.

122 South Michigan Boulevard.

185 North Wabash Avenue.

30 North Michigan Boulevard.

13. Orr, T. G., and Helwig, F. C.: The Hepatorenal Syndrome, in Frank Howard Lahey Birthday Volume, June First, Nineteen Hundred Forty, Springfield, Ill., Charles C. Thomas, Publisher, 1940, p. 339.

Progress in Internal Medicine

ALLERGY

A REVIEW OF THE LITERATURE OF 1942

FRANCIS M. RACKEMANN, M.D.
Lecturer in Medicine, Harvard Medical School; Physician, Massachusetts General Hospital
BOSTON

The field of allergy is being cultivated; also, it is being extended. The common allergic manifestations are hay fever, asthma and eczema, but other symptom complexes also may depend on allergy, and the list becomes longer as knowledge increases. More and more of the phenomena of allergy are being correlated with the phenomena of acute and chronic infections. Bacterial allergy is often hard to demonstrate, but nevertheless it undoubtedly plays a role in many difficult situations hard to understand without such a theory. Asthma often appears to be produced by acute colds and without other cause. One is almost forced to think of "bacterial allergy," but cutaneous tests made with various preparations of bacteria in the sputum do not give a reaction of immediate type, as might be encountered if the cause were ragweed or egg albumin—except in rare instances. Asthma, according to Landau and Gay,[1] has been defined by Berger as "a multiple, functional, inflammatory bronchial stenosis." This definition might implicate the mechanisms of allergy, but it implies more the effect of a particular type of sticky exudate, as will be discussed later. When more knowledge of bacterial allergy in asthma is acquired, it may be found that the two implications go together.

The recognition that periarteritis nodosa is encountered not uncommonly in association with severe types of asthma suggests that a lesion of the blood vessels is a part of the fundamental process. Certain local vascular disturbances may depend on allergy, as Harkavy[2] has shown. The Arthus phenomenon has been shown to begin with a thrombosis of small blood vessels, which leads promptly to the development of typical local necrosis.

One must consider, therefore, that lesions of the blood vessels are a part of this complex picture. The idea interferes somewhat with the earlier concept that allergy was concerned only with epithelial structures.

1. Landau, W., and Gay, L. N.: Allergy in Germany, J. Allergy **13**:494, 1942.
2. Harkavy, J.: Vascular Allergy: Manifestations of Polyvalent Sensitization, J. Mt. Sinai Hosp. **8**:592, 1942.

for now endothelial tissues seem to be involved also. The field is extended, but with good reason.

The locality of the allergic response is another important aspect. Why does a sensitiveness to egg result in eczema in one child and asthma in another? Ragweed causes hay fever often enough, but it may produce asthma without any nasal symptoms at all, and then in rare cases it can produce a local dermatitis. Elsewhere I [3] have pointed out that a review of the literature on drug allergy shows that the same medicament when taken by mouth can produce asthma in one patient, a diffuse cutaneous reaction in another or a disturbance of the blood-forming organs in a third. It would seem, therefore, that one tissue can become more sensitive than another tissue and that reactions which are localized may or may not be associated with a sensitiveness of all the tissues. Related to this idea is the observation that in certain patients seen at the very beginning of their hay fever cutaneous tests may yield quite negative results, whereas in the next year the cutaneous reactions become positive. This has been interpreted as evidence that the development of allergy in one tissue may occur before its development in other tissues. The idea explains some of the discrepancies in results of cutaneous tests, which may or may not be positive, even though the mucous membranes of the nose and the bronchi are capable of reacting so violently.

In a review of the literature of allergy of 1941 I [4] called attention to the advantages of separating the study of allergy as a problem in immunology from the study of asthma (and I include other allergic manifestations as well) as a problem in physiology. Since this distinction was made, the whole field is a bit clearer. Since the allergic reaction has been recognized as merely one of a variety of the causes of asthma, a considerable number of other causes have been recognized. Let us, however, discuss allergy first.

NATURE OF THE ALLERGIC STATE

The nature of the allergic state is still obscure, and this corner of the field needs much further cultivation.

Inheritance.—This factor is obviously important. Jacobs and his co-workers [5] have confirmed the observation of Landsteiner and Chase [6]

3. Rackemann, F. M.: Allergy, with Special Reference to Drug Allergy, New England J. Med. **224**:688, 1941.

4. Rackemann, F. M.: Allergy: Review of Literature of 1941, Arch. Int. Med. **69**:128 (Jan.) 1942.

5. Jacobs, J. L.; Kelley, J. J., and Sommers, S. C.: Heredity, Predisposition to Sensitization in Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **48**:639, 1941.

6. Landsteiner, K., and Chase, M. W.: Breeding Experiments in Reference to Drug Allergy in Animals, in Proceedings of the International Congress for Microbiology, 1940, p. 772.

that guinea pigs can be bred selectively, so as to obtain a strain which is resistant to a given allergen. From this it looks as though the factor of inheritance was concerned with the capacity of the organism for the development of local tissue antibodies, but there are other possibilities. Inheritance might be concerned with the permeability of the skin and/or of the gastrointestinal tract to make the tissues more accessible to the foreign substance, or it might be concerned with the release of H substance. And then as a fourth possibility there is the ability of the organism to react to this H substance.

Endocrine Variations.—These variations constitute another factor. So far the most promising aspect is concerned with the sex hormones in general. Pregnancy has a decided effect on hay fever and asthma, as Farmer [7] has outlined. One difficulty is that this effect is not always regular. Sometimes the symptoms are worse during pregnancy, but in other cases they clear entirely during the period of gestation. Emotional factors are receiving more attention. Stokes and Beerman [8] present a review of the problem under the title "Psychosomatic Correlations in Allergic Conditions." Jensen and Stoesser [9] point to the increasing recognition of emotional factors in asthma and cite cases in which the control of these factors helped greatly in the control of the asthma. Abramson [10] describes a woman of 31 who suffered from giant hives after swimming in cold water; when her arm was tested with ice an urticarial wheal developed at the site. At the same time she was found to be suffering from certain mental conflicts. When later these conflicts were adjusted, her sensitiveness to cold disappeared. Should one say that in her case the trouble was concerned with the quantitative development of the reaction-producing factor—the H substance, or was it concerned merely with an increased reaction to it? It is fair to anticipate that if the various factors resulting in any one response can be distinguished one from the other, the effect of emotional disturbances as well as the effect of particular endocrine variations may become more clear.

Vitamins.—These substances are interesting to the student of the nature of allergy, but recent work tends to discredit their great importance. In 1934 Sulzberger and Simon [11] found that when two series

7. Farmer, L.: The Role of the Endocrines in Anaphylaxis and Allergy, Ann. Int. Med. **17**:212, 1942.

8. Stokes, J. H., and Beerman, H.: Psychosomatic Correlations in Allergic Conditions: A Review of Problems and Literature, Psychosom. Med. **2**:439, 1940.

9. Jensen, R. A., and Stoesser, A. V.: Emotional Factor in Bronchial Asthma in Children, Am. J. Dis. Child. **62**:80 (July) 1941.

10. Abramson, H. A.: Editorial Comments: Physical or Psychic Allergy, J. A. M. A. **118**:229 (Jan. 17) 1942.

11. Sulzberger, M. B., and Simon, F. A.: Arsphenamine Hypersensitiveness in Guinea Pigs, J. Allergy **6**:39, 1934.

of guinea pigs were submitted to the same experimental procedure in an attempt to sensitize them to arsphenamine, the results in one series were quite different from those in the other, and they thought first of variations in vitamins in the fodder as the factor responsible for the difference. Frei [12] has studied this directly working especially with vitamin A (carotene), but also with the vitamin B complex and with vitamin E. Although the fodder of his animals was varied within a wide range, he could not demonstrate any significant changes in their subsequent sensitization or reaction. Feller, Roberts, Ralli and Francis [13] also worked on vitamin A, as well as on vitamin C. Marked and prolonged changes in the feeding of these components produced severe deficiencies, but neither these changes nor later flooding with vitamin excesses made any difference in the capacity of the animals to respond to a variety of immunologic tests. Meantime, however, Hochwald [14] and others have shown that the intravenous injection of ascorbic acid (vitamin C) in large quantities can protect guinea pigs against anaphylactic shock. This, however, represents the effect of ascorbic acid as a drug with its reducing action and not the effect of any vitamin lack.

Development of Sensitiveness.—The development of sensitiveness in a susceptible animal depends on the method by which the susceptible animal is exposed. One can presume that the involvement of a particular tissue resulting in particular manifestations depends on some local injury which makes that tissue absorb the antigen a little faster than other tissues. I believe that the work of Matthew Walzer deserves more attention and recognition. He [15] has recently summarized a long series of studies which show that the feeding to or the injection of a foreign substance into normal subjects (whether human beings or monkeys) is followed promptly by the absorption of the substance into the blood stream and tissues. By injecting into the skin of a subject a small dose of serum from a donor who is actively sensitized, Walzer can demonstrate that a local urticarial reaction appears in the prepared site within a few minutes after the foreign substance itself is fed or injected. This means that the foreign substance is absorbed unchanged or at least that its chemical subdivision has not progressed to any considerable extent.

---

12. Frei, W.: Further Studies in Arsphenamine Hypersensitiveness in Guinea Pigs: Vitamin A (Carotene) in Relation to the Sensitization of Guinea Pigs to Old Arsphenamine, J. Invest. Dermat. **5**:117, 1942.

13. Feller, A. E.; Roberts, L. B.; Ralli, E. P., and Francis, T.: Studies on the Influence of Vitamin A and Vitamin C on Certain Immunological Reactions in Man, J. Clin. Investigation **21**:121, 1942.

14. Hochwald, A.: Antiallergic Properties of Vitamin C, Zentralbl. f. inn. Med. **56**:769, 1935.

15. Walzer, M.: Absorption of Allergens, J. Allergy **13**:555, 1942.

I believe that this observation is of considerable importance to the whole problem of food assimilation and absorption. It is interesting that the absorption of almost any food can be demonstrated if only one can find a donor who is specifically sensitive to that particular substance and whose serum has a sufficiently high reaginic titer toward it. Walzer shows that the reaction in the prepared site occurs within less than ten minutes and that it can be produced by minute quantities of the offending substance. How long the reaction will persist or how long the offending substance will remain in circulation or in the tissues has not yet been worked out. Walzer has demonstrated a method by which active sensitiveness of the tissues might occur. Meantime, Hartley [16] has been able to sensitize guinea pigs by single feedings of small quantities of egg albumin—and the results were better if the intestinal mucosa was injured a little by the withholding of vitamin C and the production of scurvy. Incidentally, he found that if the feeding was continued, the circulating antibodies which were demonstrable at first disappeared, and this fact helps one to understand why it is that not all persons are sensitive to all foods all the time.

The newborn babe is not sensitive. Hill and Sulzberger [17] showed this some years ago. And now Zohn [18] has tested 150 infants from 3 to 8 days of age with egg, wheat and milk and failed to obtain any positive reaction. Histamine, however, when injected in a dilution of 1:10,000, caused wheal formations consistently. Evidently the development of allergy depends on antibodies, and antibodies require time for production.

Development of Sensitiveness from Contact.—Criep [19] studied 7 pairs of identical twins, and only 3 of them behaved quite alike. In 1 pair, 1 twin had hay fever in June from grasses and the other had hay fever in August from ragweed. In another pair, the onset was at 3 and at 4 years, respectively, and finally, a sensitiveness to acetylsalicylic acid developed in 1 of a pair, whereas a sensitiveness to egg developed in the other. As Criep says: "Contact is important, but one must explain the absence of sensitiveness to many common allergens." Just why one substance should be seized on to the exclusion of all the others is a question hard to answer. That nursing mothers can absorb undigested proteins

16. Hartley, G., Jr.: The Permeability of the Gastro-Intestinal Mucosa of Guinea Pigs to Crystalline Egg-Albumin: II. Relationship Between Circulating-Antibody Titer and Severity of the Anaphylactic Shock Following the Oral Administration of Antigen to Actively Immunized Scorbutic and Non-Scorbutic Guinea Pigs, J. Immunol. **43**:301, 1942.

17. Hill, D. W., and Sulzberger, M. B.: Evolution of Atopic Dermatitis, Arch. Dermat. & Syph. **32**:451 (Sept.) 1935.

18. Zohn, B.: Skin Testing in the Newborn, Arch. Pediat. **58**:339, 1941.

19. Criep, L. H.: Allergy in Identical Twins: Report of Seven Pairs of Twins, J. Allergy **13**:591, 1942.

and excrete them in their milk was shown by Donnally [20] in 1930. Cutaneous sites in normal persons made sensitive by intradermal injections of serum from a person sensitive to eggs would react to a tiny quantity of milk from a mother who had just eaten several eggs. In a similar experiment Brunner and Baron [21] illustrate the same principles for cotton seed. Also, they show that specimens of milk taken during the first two hours after the ingestion of cotton seed contain little or no antigen, but that a longer time—two and one-half to twenty-four hours—was required before the test meal gave definitely positive results. The delay in this experiment is hard to explain. Courtright and his associates [22] have worked on guinea pigs sensitized by exposure to the dust of dry horse dander. This experiment was made first in 1925 by Ratner and others.[23] The present authors were interested particularly in the protection of their animals by histamine and histaminase. The study is mentioned here to remind the reader that sensitiveness can occur by the inhalation of dust and that in clinical practice one finds this form of sensitiveness to be much more important than any other. Cannon and his associates [24] produced symptoms in sensitized animals by dropping a solution of purified egg albumin into their noses. A marked pulmonary inflammation was produced in all of them, and it is interesting to have Cannon lay some stress on the development of phlebitis and thrombosis—vascular phenomona—as part of this reaction process.

The small amount of contact which is necessary to produce sensitiveness is always interesting. In 1924 Hooker [25] showed that 33 per cent of young subjects who had been given intracutaneous test doses of diphtheria toxin–antitoxin mixtures became skin sensitive to horse serum later. The term skin sensitive is used advisedly. The change may or may not be accompanied by the development of a general sensitiveness.

Recently, Baron and Brunner [26] reported much the same thing for Trichina antigen. Eighteen patients were given injections of small

20. Donnally, H. H.: The Question of the Elimination of Foreign Protein (Egg White) in Woman's Milk, J. Immunol. **19**:15, 1930.

21. Brunner, M., and Baron, B.: The Presence of Ingested Cottonseed Protein in Woman's Milk, J. Allergy **13**:358, 1942.

22. Courtright, L. J.; Hurwitz, S. H., and Courtright, A. B.: Inhalant Sensitization and Shock in Guinea Pigs Under Controlled Atmospheric Conditions, J. Allergy **13**:444, 1942.

23. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: Nasal Sensitization, Nasal Anaphylactic Shock and Respiratory Symptoms Simulating Bronchial Asthma in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **23**:17, 1925.

24. Cannon, P. R.; Walsh, T. E., and Marshall, C. E.: Acute Local Anaphylactic Inflammation of the Lungs, Am. J. Path. **17**:777, 1941.

25. Hooker, S. B.: Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum, J. Immunol. **9**:7, 1924.

26. Baron, B., and Brunner, M.: Active Sensitization in Human Beings with Trichina Antigen, J. Allergy **13**:459, 1942.

quantities (0.10 cc.) of the antigen every one or two weeks. In 10 of them an immediate positive reaction developed to one or another of the later doses—to the third dose in 2 patients, to the fourth in 1, to the fifth in 3, to the sixth in 1, to the seventh in 1, to the eighth in 1 and to the ninth in 1. They make the good point that the diagnostic value of tests like this diminishes with repetition. Arbesman, Witebsky and Osgood [27] draw similar conclusions after making tests with Trichina antigen on 28 consecutive patients with allergy and 91 consecutive normal persons. The incidence of positive reactions was as much as 22 per cent in the allergic group.

Two papers are concerned with the nature of the sensitizing substance. Spain, Gillson and Strauss [28] compared the production of sensitiveness and the subsequent reaction to extracts of serum, saliva and skin epithelium of the dog, cat and the rabbit. On the whole, a guinea pig sensitized to dog saliva reacts well to dog serum or to dog epithelium, and this fact shows that a common antigenic factor is present in the three preparations. The same thing applies to rabbit saliva, serum and epithelium. But there are certain exceptions which suggest that there may be specific factors as well and that saliva, serum and skin substance are not the same in every particular. The other paper is by Cooke,[29] who reviews his work on protein derivatives of common foods. In food allergy it is not usual to encounter cutaneous reactions which correspond with the history of the patient. The diagnosis is made on the basis of trial and error, as brought out by the patient's direct personal experiences. Cooke has considered that the process of digestion results in the production of intermediary substances which are the actual cause of the sensitiveness and of the symptoms. The idea is important, and Cooke has assembled a good deal of experimental work to support it.

HISTAMINE

In the recent review of the literature on anaphylaxis by Dragstedt [30] the last paragraph includes this sentence:

> The cardinal symptoms of anaphylaxis can thus be explained as being due, in the immediate instance, to an autointoxication by physiologically active substances normally resident in various tissue cells and liberated therefrom by some change in cellular permeability brought about by the antigen-antibody reaction.

27. Arbesman, C. E.; Witebsky, E., and Osgood, H.: Results of Intradermal Skin Tests with Trichina Antigen in Allergic and Normal Individuals, J. Allergy **13**:583, 1942.

28. Spain, W. C.; Gillson, R. E., and Strauss, M. B.: Comparative Immunologic Studies with Salivary and Epithelial Extracts of the Dog, Cat and Rabbit, J. Allergy **13**:563, 1942.

29. Cooke, R. A.: Protein Derivatives as Factors in Allergy, Ann. Int. Med. **16**:71, 1942.

30. Dragstedt, C. A.: Anaphylaxis, Physiol. Rev. **21**:563, 1941.

It is assumed that in clinical allergy in man the symptoms depend on the release from normal cells of a normal cellular constituent. In another paper from Dragstedt's laboratory, by Ojers and others,[31] sections of the liver were removed from dogs during anaphylactic shock and tested for their histamine content. The authors found that the amount of histamine liberated was quite enough to account for this shock symptom. Dragstedt and Silva[32] added trypsin to heparinized rabbit blood and found that it caused a shift in the histamine from the cells to the plasma.

Treatment of Patients with Histamine.—This procedure is sometimes effective in allergy, but reports, past and present, are not in agreement as to the percentage of good results, and in some cases the method seems to be totally ineffective. Wells, Gray and Dragstedt[33] tested the method on dogs. If a real tolerance to histamine can be produced, one would expect that the secretion of acid from the dog's stomach would become less as the daily dose of histamine is continued. The authors worked with dogs the stomachs of which were prepared to produce the so-called "Heidenhain pouch." They found that when the nourishment of the dogs was good, the response to repeated doses of histamine remained quite the same even after a long series of injections. A reduction in the response occurred only in those dogs the general condition of which had suffered. The authors could not provide experimental analogy for the therapeutic effect claimed for histamine desensitization in allergy. Sheldon and his co-workers[34] believed that treatment with histamine might be more effective if the substance could be made antigenic by combining it with a protein, and so such preparations as histamine azocasein and a combination of histamine and azo despeciated horse serum globulin were made in the laboratory and used for the treatment of a series of patients. Good results were obtained in some cases, but, as the authors explained, there is no evidence that these results were on a specific basis or that they differed from other results produced by vaccines and other substances. The theory that histamine is the end product of a great variety of specific reactions is always attractive, but so far it is still hard to be sure of its correctness.

---

31. Ojers, G.; Holmes, C. A., and Dragstedt, C. A.: The Relation of the Liver Histamine to Anaphylactic Shock in Dogs, J. Pharmacol. & Exper. Therap. **73**: 33, 1941.

32. Dragstedt, C. A., and Roche e Silva, M.: Effect of Trypsin upon Blood Histamine of Rabbits, Proc. Soc. Exper. Biol. & Med. **47**:420, 1941.

33. Wells, J. A.; Gray, J. S., and Dragstedt, C. A.: An Investigation of the Question of Histamine Tolerance, J. Allergy **13**:77, 1941.

34. Sheldon, J. M.; Fall, N.; Johnston, J. H., and Howes, H. A.: A Clinical Study of Histamine-Azo-Protein in Allergic Disease: A Preliminary Report, J. Allergy **13**:18, 1941.

Acetylcholine—This is another substance which is normally present in the body cells and which might well be the factor released by specific reactions. It differs from histamine in some ways, but its cholinergic effect is not dissimilar. Acetylcholine itself is labile. It is destroyed by heat; it is destroyed by standing, and it disappears promptly when it is injected into the organism. On the other hand, its methyl derivative has much the same pharmacologic properties and is used rather widely in certain fields of medicine. Moll [35] has used it in the treatment of asthma. In doses of 10 to 20 mg. given to patients with asthma mecholyl chloride (acetylbetamethylcholine hydrochloride) produced wheezing, which was usually mild but sometimes severe. In a series of nonasthmatic control subjects who received doses of the same size, symptoms referable to the chest were not observed, but general signs of parasympathetic stimulation did occur. This last observation is not surprising, because in other patients hay fever or eczema or even urticaria has been lit up in a new attack by substances other than the precise specific causative one. The experience is used by some investigators to suggest that a sort of conditioned reflex is involved in the mechanism, but better perhaps is the concept that different tissues vary in the degree of their sensitiveness. Logue and Laws [36] treated 11 patients suffering from chronic asthma with mecholyl chloride and found that 6, or about a half, were improved by a series of ten daily doses. Fortunately, however, 6 other patients with chronic asthma were treated in the same way and at the same time with doses of physiologic solution of sodium chloride, and 4 of these, or two-thirds, were greatly improved. Another good experiment has been spoiled by controls!

Histaminase.—This substance is not as interesting as it appeared to be some year ago. Hawes, Alles and Miller [37] have repeated the original experiments of Karady and Brown, who found that anaphylactic shock in guinea pigs could be controlled by histaminase. The California investigators, however, had completely negative results. In their hands histaminase had little value. Neely [38] believes that allergic asthma in guinea pigs might provide a good method of measuring the effect of histaminase on the reaction. A small series of animals were treated with histaminase given in various ways during the period of sensitization and just before, as well as just after, the shock dose. No protective effect, however, was observed.

35. Moll, H. H.: The Action of Parasympathetic-Mimetic Drugs in Asthma, Quart. J. Med. **9**:229, 1940.

36. Logue, R. B., and Laws, C.: Mecholyl (Acetyl-β-Methyl-Choline) Desensitization, J. Allergy **13**:414, 1942.

37. Hawes, R. C.; Alles, G. A., and Miller, H.: Question of Protection Against Histamine and Anaphylactic Shock in Guinea Pigs by Histaminase, J. Lab. & Clin. Med. **27**:337, 1942.

38. Neely, F. L.: Treatment with Histaminase, J. Lab. & Clin. Med. **27**:319, 1941.

SERUM DISEASE AND SERUM ACCIDENTS

In reviewing the problems of allergy in wartime Vaughan [39] notes that one has learned to respect the story of the patient who says he has horse asthma and so not to put him in the cavalry. One has learned that hay fever may be severe or mild, incapacitating on the one hand and only a slight nuisance on the other—and I can add that the distinction is determined by the history and clinical experience and has little to do with the size of any cutaneous reaction which might be observed. And finally the Army and Navy have learned about serum sensitiveness. Kojis [40] has presented a careful and complete analysis of 6,211 patients who were treated with horse serum for various reasons. He comments on the 5 patients, or just under 0.10 per cent, who died suddenly after the treatment, evidently because they were naturally sensitive to the foreign protein; they were allergic persons. Kojis describes the factors which influence the incidence of serum disease: the age and sex of the patient, the kind of serum and particularly the amount injected and the route by which it is given. He describes the many symptoms which may be included under the designation of serum disease; rashes are most common, but fever may occur by itself. Enlargement of the lymph glands, swelling of the joints, edema of the subcutaneous tissues and then, finally, various mental and nervous complications can all appear. The Arthus phenomenon with its local necrosis beginning at the site of inoculation is rare, but nevertheless it is a dramatic result which may be serious. And then finally Kojis describes the various methods by which the presence of sensitiveness to horse serum can be anticipated and by which the specific treatments which appear so necessary can be given even in the presence of this sensitiveness. It is a useful and timely paper.

In a shorter article Rackemann [41] calls attention to the three types of serum reactions: serious, sometimes fatal reactions in those allergic persons who never have had serum before; severe and sometimes fatal reactions in those persons who have had a preliminary dose of serum within a short time and so are actively sensitized, just like the guinea pig in the laboratory equipment (and here one can add that when more serum is given during the height of serum disease or within a few days after its subsidence, fatal reactions are particularly prone to occur), and

39. Vaughan, W. T.: Problem of Allergy in Wartime, Mil. Surgeon **89**:737, 1941.

40. Kojis, F. G.: Serum Sickness and Anaphylaxis: Analysis of 6,211 Patients Treated with Horse Serum for Various Infections, Am. J. Dis. Child. **64**:93 (July) 1942.

41. Rackemann, F. M.: Medical Progress; Allergy: Serum Reactions, with Particular Reference to the Prevention and Treatment of Tetanus, New England J. Med. **226**:726, 1942.

serum disease proper, which after all is a normal response of a normal person. Toomey and Garver [42] present results obtained on 1,447 patients who were given cutaneous tests and ophthalmic tests just before the injection of diphtheria antitoxin. Serum sickness occurred in about 30 per cent of those who had had antitoxin previously and regardless of whether the cutaneous reactions were positive, but serum sickness occurred in 48 per cent of those who showed positive ophthalmic reactions. It occurred in only 23 per cent of those whose ophthalmic reactions were negative.

I would emphasize that if one recalls the difference in susceptibility between three groups of patients—first, the allergic persons with histories of hay fever or asthma; second, the pretreated patients who may be actively sensitive, and, third, the normal persons with neither allergy nor previous treatment—it is quite clear that to ask one or two simple questions of the patient may bring more useful information than any cutaneous test.

Plasma.—This substance is not quite free of reaction possibilities. Polayes and Squillace [43] described the severe reaction with chills and shock which occurred when a woman of 29 was given 250 cc. of dried normal human plasma shortly after childbirth. An editorial [44] in *The Journal of the American Medical Association* comments on this report to say that if cutaneous tests with samples of plasma could be made, reactions would be avoided. What can be done when a cutaneous test or an ophthalmic test made with a sample of the serum about to be injected (or better, with a 1:10 dilution of it in normal physiologic salt solution of sodium chloride) is found to yield a positive reaction? Glaser [45] finds that bovine tetanus antitoxin given to 38 children, half of whom were known to be allergic, did not cause any immediate reactions at all and produced serum disease in only about 40 per cent. Top and Watson [46] used antitoxin which had been "despeciated" by enzymic digestion. They gave this preparation to 130 patients; reactions of all kinds were greatly reduced, and certain persons who could not tolerate the usual refined or concentrated antitoxin were successfully treated with this new product. Attention should be called to a recent paper by

42. Toomey, J. A., and Garver, W. P.: Sensitivity to Horse Serum Due to Previous Injections of Antigen, Am. J. Dis. Child. **62**:765 (Oct.) 1941.

43. Polayes, S. H., and Squillace, J. A.: Near Fatal Reaction to Transfusion with Dried Human Plasma Solution, J. A. M. A. **118**:1050 (March 28) 1942.

44. Toxicity of Human Plasma, editorial, J. A. M. A. **120**:206 (Sept. 19) 1942.

45. Glaser, J.: The Use of Bovine Antitoxin for the Prophylaxis of Tetanus, J. Pediat. **19**:403, 1941.

46. Top, F. H., and Watson, E. H.: Reduction of Serum Reactions, Am. J. Dis. Child. **62**:548 (Sept.) 1941.

Simon [47] which brings out two interesting points. Simon finds that hypersensitiveness to mammalian serum is only in part species specific. The serum of some sensitive persons will neutralize the antibodies (reagins) for many other mammalian serums, but the serum of others will neutralize the antibodies only for itself and perhaps for one or two other mammals. The possibility that among the larger land mammals is an antigenic factor which is common—a group-specific antigen, as well as the more typical species-specific antigen—is suggested. Simon points out that different human beings react to the same serum complex differently, just as Landsteiner could show that of two chemicals applied to the human skin, certain persons will become sensitive to one, others to the second and some to both. The other suggestion—that the so-called "natural" sensitiveness to horse serum which is sometimes observed in persons who give no history of previous contact with the substance may depend on the common group-specific antigen derived perhaps from eating meat of various kinds—is attractive.

Reactions to tetanus toxoid have been greatly reduced by improvements in the method of preparing the material. The details are described in Rackemann's article already mentioned.[41] Peshkin [48] treated 65 children known to be allergic to various substances with the combined alum-precipitated diphtheria and tetanus toxoids. Local reactions occurred in 25 per cent, but constitutional reactions were not observed. The antitoxin titer rose to satisfactory levels. Incidentally, the following report is of interest: Zuger, Greenwald and Gerber,[49] of the New York Department of Health, treated two groups of guinea pigs, 75 in each, with two doses of alum-precipitated tetanus toxoid and then inoculated the animals with tetanus spores. In the group which received an additional booster dose of toxoid at the time of inoculation, 8 animals had local tetanus, and none died. In the other group, however, without the booster dose, 13 animals had local tetanus and 4 had generalized tetanus.

HAY FEVER

Pollen Surveys.—These surveys, including daily pollen counts, are exciting the interest of persons who would like to get rid of all pollen-producing plants by pulling them up. The state of Michigan [50] began

47. Simon, F. A.: Human Allergy to Mammalian Sera, J. Exper. Med. **75**: 315, 1942.

48. Peshkin, M. M.: Immunity to Tetanus Induced by Combined Alum-Precipitated Diphtheria and Tetanus Toxoids, Am. J. Dis. Child. **62**:309 (Aug.) 1941.

49. Zuger, B.; Greenwald, C. K., and Gerber, H.: Tetanus Immunization: Effectiveness of the Stimulating Dose of Toxoid Under Conditions of Infection, J. Immunol. **44**:309, 1942.

50. Ragweed Pollen Count, Medical News (Michigan), J. A. M. A. **119**:959 (July 18) 1942.

this summer a third pollen survey with observers at forty-four stations, and other communities, will, no doubt, undertake similar studies after the war. From sixty-four replies to a questionnaire on pollen sent to all members of the Society for the Study of Asthma and Allied Conditions, Vander Veer and associates [51] have compiled a preliminary record of the pollen which occurs in New England. It shows the pollination seasons of trees, grasses and ragweed, and it indicates the minor variations which occur from place to place. The final report should be an important addition to present knowledge. Stroh [52] has added a new survey of the pollen over Seattle and its vicinity, and from Brazil comes a report by Greco and others [53] in the state of Minas Geraes, which is on the southeastern side of Brazil and just north of Rio de Janeiro. In that state it rains from September 15 to April 15 (in the northern hemisphere these dates would be March 15 to October 15), but then the grasses come out and grow profusely until June 15 (December 15 in this hemisphere). What hay fever there is comes merely for a short time from these grasses. Phillips [54] has studied the pollen over South Australia.

Chemistry of Pollen.—This factor presents an important problem difficult of solution. An excellent and a complete survey of the literature available to January 1942 has been presented by Newell.[55] So far it has not been possible to isolate the "skin-sensitizing principle" in pure form. In 1939 Stull and Sherman [56] found that extracts precipitated by half saturation with ammonium sulfate contained mostly albumin, whereas another extract precipitated by full saturation contained globulins. Both types of extract were skin-test-active,[56a] and both could neutralize the antibodies in the serum of ragweed-sensitive patients. Now Sherman

51. Vander Veer, A. H.; Barnard, I. M.; Cunningham, T. D.; Nelson, T.; Pratt, H. N., and Simon, F. A.: Report of the Committee on a Pollen Survey of the United States: The Society for the Study of Asthma and Allied Conditions, J. Allergy **13**:516, 1942.

52. Stroh, J.: Flora and Pollen Surveys of Seattle and Vicinity, Northwest Med. **39**:258, 1940.

53. Greco, J. B.; Lima, A. O., and Tupinamba, A.: The Pollen Content of the Air in Belo Horizonte, Brazil, J. Allergy **13**:411, 1942.

54. Phillips, M. E.: Studies in Atmospheric Pollen, M. J. Australia **2**:189, 1942.

55. Newell, J. M.: A Review of Chemical Studies on the Allergens in Pollens, J. Allergy **13**:177, 1942.

56. Stull, A., and Sherman, W. B.: Further Studies on the Allergenic Activity of Protein and Nonprotein Nitrogen Fractions of Ragweed Pollen Extract, J. Allergy **10**:130, 1939.

56a. "Skin-test-active" means capable of eliciting a positive cutaneous reaction in a patient already sensitized.

and Hebald [57] find that constitutional reactions following treatment are more likely to occur in those patients who give strong cutaneous reactions to the globulin fraction, with or without reaction to albumin at the same time. Treatment of this group is difficult, but it can be successful if the pollen doses are regulated with care. They have to be kept small in most cases. Stull, Sherman and Wing [58] find that extracts prepared with water or with solutions of sodium bicarbonate or sodium hydroxide behaved differently as far as cutaneous tests and neutralization tests were concerned. It is evident that different methods of extraction produce materials which have slightly different reactions.

Roth and Nelson [59] find two protein fractions in ragweed pollen. One is of large molecular size and is responsible for the precipitin reaction with rabbit antiserum. The fraction of small molecular size produces the cutaneous reaction in human subjects. When a sample of pollen was extracted repeatedly with water, the later extracts no longer produced a cutaneous reaction, but the residue was still high in its nitrogen content and potent in its ability to produce immune reactions. Abramson and his co-workers [60] have studied pollen by electrophoresis. When a small current of electricity is passed through a solution of proteins those elements which are negatively charged go in one direction and those which are positively charged in another. Ragweed contains a major component which is negatively charged, is colorless, produces extensive cutaneous reactions and causes symptoms. It migrates slowly. Of less importance is a smaller molecule which is pigmented and moves rapidly toward the negative pole. It carries a positive charge. The difficulty is that this also is a skin-sensitizing substance.

In a paper to be published Newell [61] demonstrates, first, that the components separated by electrophoresis are not pure and, second, that each of them studied so far gives a cutaneous reaction test to greater or less extent. Rockwell [62] describes a preparation of ragweed pollen which can be precipitated by hydrochloric acid which he claims is pure

57. Sherman, W. A., and Hebald, S.: A Method of Determining the Probability of Constitutional Reactions During Treatment of the Ragweed Hay Fever Patient, Am. J. M. Sc. **203**:383, 1942.

58. Stull, A.; Sherman, W. B., and Wing, W. M.: Antigenic Fractions in Ragweed Pollen, J. Allergy **13**:537, 1942.

59. Roth, R. R., and Nelson, T.: Proteins of Ragweed Pollen, J. Allergy **13**: 283, 1942.

60. Abramson, H. A.; Moore, D. H., and Gettner, H. H.: Electrophoretic and Ultracentrifugal Analysis of Hay-Fever-Producing Component of Ragweed Pollen Extract, J. Phys. Chem. **46**:192, 1942.

61. Newell, J. M.: Electrophoretic Studies on the Chemical Fractionation of Ragweed Pollen Extracts, to be published.

62. Rockwell, G. E.: Studies on Chemical Nature and Standardization of Pollen-Antigen, J. Immunol. **43**:259, 1942.

and consists of a polypeptide carrying a large percentage of basic amino acid. Treatment with this material gave good results in a moderate number of cases.

Taub and Rubens [63] made an aqueous solution of ragweed which was frozen and dried *in vacuo* and then taken up in sesame oil with the idea that absorption would be slow and the effect more prolonged. So far, the authors have not found any reports of sensitizations to sesame oil, and the preparation seems to keep well, remaining unchanged for over a year. However, I am not too enthusiastic about oily preparations.

Treatment of Hay Fever.—This has not been advanced much. The mechanism of the good results remains obscure, and the only real fact is that each year an ever increasing number of patients apply to clinics for treatment and that a certain proportion of these patients report at the end of the season that they have been much more comfortable than usual. The technic of treatment varies widely in different clinics. Golan, Hill and Sack [64] compare the effects of preseasonal and coseasonal treatment, on the one hand, and preseasonal treatment alone, on the other. The results were substantially the same in the two groups, and they conclude that little was to be gained by continuing the specific therapy during the pollen season. Markow and Rosen,[65] on the other hand, had better results with perennial than with preseasonal methods. Stoesser,[66] of the University of Minnesota, has analyzed his results and declares that long preseasonal or perennial therapy is the best.

The study of oral therapy with pollen has been continued. Iliff and Gay [67] present a table of all the results previously reported in the literature, commenting on their wide divergence. When ragweed pollen was given in large repeated doses (500 to 250,000 Noon units, or 0.50 to 250.0 mg.) before the season, the results were not nearly so good as those in another series of patients who were treated by the conventional hypodermic method. The results were good in only 13 of 62 patients treated by oral doses before the season, and in none of the 20 patients treated during the season were there any good results at all. Furthermore, abdominal pain, nausea and other reactions were encountered. Of the group of 37 patients treated by hypodermic injection in the same

63. Taub, S. J., and Rubens, E.: A Preliminary Report on the New Slowly Absorbed Medium for Use in Hay Fever Treatment, J. Allergy **13**:138, 1942.

64. Golan, H. G.; Hill, R., and Sack, S. S.: The Value of Continuing Preseasonal Therapy During the Pollen Season, J. Allergy **13**:300, 1942.

65. Markow, H., and Rosen, E. A.: Comparison of Results of Preseasonal and Perennial Methods of Treatment of Ragweed Hay Fever, M. Rec. **155**:203, 1942.

66. Stoesser, A. V.: Recent Observations on Hay Fever in Children, Journal-Lancet **62**:174, 1942.

67. Iliff, E. H., and Gay, L. N.: Oral Treatment with Ragweed Pollen, Bull. Johns Hopkins Hosp. **70**:378, 1942.

season, good results were obtained in 24. The oral treatment cannot compare with the subcutaneous method. As for "coli metabolin" (filtrate of Escherichia coli [Tosse]), Loveless and Baldwin [68] studied it carefully but found that "the transient benefits were duplicated in degree and duration by injections of saline." Meantime, the treatment of hay fever is not a simple or casual procedure to be undertaken without proper consideration. Francis [69] took care of a young married woman who suffered a severe general reaction after an injection of grass pollen which resulted in an abortion of her pregnancy. Colmes [70] has followed a number of patients who gave histories quite typical of ragweed hay fever but in whom cutaneous tests were always negative. Ophthalmic tests, however, yielded positive reactions in many of them, and the results of nasal tests made by the insufflation of dry pollen were positive in several. Treatment was given in large doses, and good results were obtained in over half the patients. Meantime, it is interesting that general constitutional reactions of slight degree were observed in 5 patients. Here is another illustration of the discrepancies which are observed frequently. Even though the cutaneous reaction is slight, the occurrence of constitutional reaction shows that the patient is sensitive nevertheless.

Hay fever is the typical form of allergic manifestation. It is a common disease. It seems almost pathetic that one knows so little about its mechanism and especially about the method by which the good results in treatment are obtained. One feature is impressive: that the gross results reported from those clinics which treat a large number of patients show about the same percentage figures. These results are excellent in about 20 per cent of cases; they are good in another 60 per cent, and they are poor in about 20 per cent, and this despite the fact that different pollen material, different kinds of extract and different technics of treatment are employed. The field is open, and if this portion of it can be cultivated, the harvest will be abundant.

Fungus Spores.—These can also cause hay fever. During the last year several excellent papers have been presented. Durham [71] gives an excellent scholarly bibliography with a historical survey of the whole mold problem, including a five year survey of the mold Aspergillus in

68. Loveless, M. H., and Baldwin, H. S.: "Coli Metabolin" Therapy in Hay Fever: Psychogenic Benefits, J. A. M. A. **118**:451 (Feb. 7) 1942.

69. Francis, N.: Abortion After Grass Pollen Injection, J. Allergy **12**:559, 1941.

70. Colmes, A.: Pollen Disease in the Absence of Positive Skin Tests, New England J. Med. **225**:817, 1941.

71. Durham, O. C.: Air-Borne Fungus Spores as Allergens, Publication 17, American Association for the Advancement of Science, New York, Doubleday, Doran & Company, 1942, vol. 32.

Chicago. Morrow, Lowe and Prince [72] have collaborated in a study of the molds recovered in various parts of central and southwestern United States. Certain molds, like Aspergillus and Penicillium, occur everywhere and are present at almost all times of the year, including the northern stations during cold weather. Other molds, however, like Alternaria and Hormodendrum, have a more definite seasonal fluctuation. The individual seasons, however, vary considerably from year to year, and the molds vary much more than do the pollens. In Texas the curves of the mold counts are rather flat, whereas in the northern area sharp peaks occur, evidently dependent on changes in wind currents, weather and dampness. It is interesting that on one occasion molds were recovered from the air immediately after a heavy fall of snow and several days of near zero weather. Bernstein and Feinberg [73] have also studied the molds in the Chicago air and for a total period of five years. They agree that individual fungi vary widely in their relation to seasons and weather, the incidence of some having relatively little relation to the time of year. It begins to look as though molds were of even greater importance than has been appreciated.

I would like to go back to an observation which was made by Rackemann, Randolph and Guba [74] in 1938 that in the case of the mold Cladosporium a well marked species specificity was clearly demonstrated in a small group of patients. Since then cutaneous tests with the products of stock mold cultures have been made in many clinics and with results which are not always clearcut and distinct. The results are suggestive rather than clearly positive. I wonder whether this observation may not be important after all, that a much higher degree of specificity exists among the molds than has been so far appreciated. On the other hand, I and many others have tested patients not only with a single strain of Alternaria, for example, but with a number of stock strains at the same time and yet have not encountered variations in the reactions which might be called striking. The concept of a high degree of specificity is interesting, but so far at least it cannot be demonstrated in any number of patients. The whole problem concerning the importance of fungi in allergy of the respiratory tract needs further study. Waldbott and his assistants [75] found that cutaneous reactions to molds

72. Morrow, M. B.; Lowe, E. P., and Prince, H. E.: Mold Fungi in Etiology of Respiratory Allergic Diseases: Survey of Air Borne Molds, J. Allergy **13**: 215, 1942.

73. Bernstein, T. B., and Feinberg, S. M.: Air-Borne Fungus Spores: Five Year Survey of Daily Mold Spore Content of Chicago Air, J. Allergy **13**:231, 1942.

74. Rackemann, F. M.; Randolph, T. G., and Guba, E. F.: The Specificity of Fungous Allergy, J. Allergy **9**:447, 1938.

75. Waldbott, G. L.; Blair, K. E., and Ackley, A. B.: An Evaluation on the Importance of Fungi in Respiratory Allergy, J. Lab. & Clin. Med. **26**:1593, 1941.

were positive in 69 per cent of a large group (841) of allergic patients. But in spite of this they confess that allergy of the respiratory tract due to one single fungus is rare, and it would seem likely that their observations are based on cutaneous reactions which are not as clearcut and sharp as one would like to see. Perhaps the technic of making extracts is faulty. Pratt,[76] for example, finds that when the spores and the mycelial threads of Alternaria were each obtained in a relatively pure state, cutaneous tests made with spore extracts gave a much greater reaction than did the tests with mycelial extracts. Crossed experiment showed that spore extracts could sensitize to mycelial extracts, but per contra mycelial extracts had no effect on sensitiveness to spores.

ASTHMA

Last winter at the meeting of the American Society for the Study of Asthma and Allied Conditions, Dr. T. B. Mallory showed a chart illustrating the mode of death of 50 patients suffering with severe asthma who had come to autopsy at the Massachusetts General Hospital. Each patient was represented by a horizontal line which began at the age of onset and ended at the age of death. The chart as a whole demonstrated three points: First, when asthma begins in childhood and before the age of 20, life runs its usual course, and death occurs some time after the age of 50 and is caused ordinarily by pneumonia or by heart disease; at least it is not due to asthma. Second, when asthma begins in early middle age, between the ages of 30 and 40, it may be complicated by periarteritis nodosa, and on the chart were represented 5 patients with this disease, which makes the rather high incidence of 10 per cent for periarteritis nodosa in severe asthma. Third, the chart showed that when asthma begins late in life, after the age of 45, the course of the disease may be short and death may occur from asthma within as little as two or three years after the onset. Does this mean that every patient in whom asthma begins after the age of 45 is doomed to die soon? It is this study of the pathologic aspects which has led to a careful follow-up of end results, which will be analyzed and published in the future.

I [77] am convinced that "intrinsic asthma" is a special type of asthma which has nothing to do with allergy in the ordinary sense. Attempts to associate the disease with contact with any particular dust or food substance are quite unavailing. The clinical history of patients with this type of asthma cannot be explained in any such easy fashion. Bacterial asthma it might be—dependent on a hypersensitiveness to the products of bacterial action in some form of infection. This again is

76. Pratt, H. N.: The Comparative Atopic Activity of Alternaria Spores and Mycelium, J. Allergy **13**:227, 1942.

77. Rackemann, F. M.: Intrinsic Asthma: Further Observations, J. Allergy **13**:622, 1942.

hard to prove except in a few isolated cases. The bronchial spasm could be a conditioned reflex from some disturbance of the nose and sinuses, but this idea is likewise hard to demonstrate except in a few particular cases. Nervous factors are present, but whether they are the cause of the process or merely the result of it is hard to say. Finally come the theories concerning endocrine substances and vitamins, which so far are only suggestions. Here is another problem, another portion of the field which is wide open and full of stones.

True Pathologic Causes of Asthma.—This type of cause is being recognized more and more—as suggested in the opening paragraphs of this review. This is not the place for any analysis of the large literature, but attention can be called to certain papers. Carcinoma can involve any portion of the lung, and the symptoms will vary in accordance with its location, particularly if the wall of the bronchus is involved. A paper by Holmes [78] contains two schematic diagrams which give the whole story in a clear and simple manner. Prickman and his associates [79] describe 3 patients who complained primarily of asthma but whose wheezing was due to carcinoma of the bronchus. Nofsinger and Vinson [80] had a patient whose cough and wheeze seemed to originate on the right side of his thorax. He had no pain, and he did not expectorate blood, but what he had was an intrabronchial metastasis of hypernephroma. The literature on cancer of the lung is reviewed by Perrone and Levinson [81] in a helpful article. In bronchiectasis the sputum is thin and watery; it is not often viscid and tenacious. Patients with this condition complain of cough, and occasionally they wheeze. In asthma, however, the sputum does not flow freely. It is tenacious and is highly viscid. Patients with asthma wheeze, and occasionally they cough. It is interesting to consider that the difference between the two groups depends chiefly on the physical characteristics of the bronchial exudate. The natural history of bronchiectasis is described in a scholarly paper by Ogilvie.[82] Pulmonary fibrosis may cause increasing dyspnea. In 2 cases described by Linenthal [83] autopsy revealed changes in small blood

78. Holmes, G. W.: Carcinoma of the Bronchus, New England J. Med. **227:** 503, 1942.

79. Prickman, L. E.; Maytum, C. K., and Moersch, H. J.: Asthma and Primary Carcinoma of Bronchus, J. Allergy **13:**261, 1942.

80. Nofsinger, C. D., and Vinson, P. P.: Intrabronchial Metastasis of Hypernephroma Simulating Primary Bronchial Carcinoma, J. A. M. A. **119:**944 (July 18) 1942.

81. Perrone, J. A., and Levinson, J. P.: Primary Carcinoma of the Lung (Report of One Hundred and Fifteen Cases, Thirty-Eight Autopsies and Seventy-Seven Bronchoscopic Biopsies), Ann. Int. Med. **17:**12, 1942.

82. Ogilvie, A. G.: The Natural History of Bronchiectasis, Arch. Int. Med. **68:** 395 (Sept.) 1941.

83. Linenthal, H.: Observations Concerning Pulmonary Fibrosis in Raynaud's Disease, J. M. Soc. New Jersey **227:**433, 1942.

vessels, and one wonders whether these can be related to the other changes observed in periarteritis nodosa. And then finally emphysema may itself cause asthma, a wheeze which complicates the ever increasing dyspnea. This is the common type of "pulmonary insufficiency," a process which makes the lungs as a pair of bellows inefficient and unable to carry on their normal function. "The Vanishing Lung" is the interesting title which Allison [84] uses to describe the insidious slow increase of the destruction of the structure and the function of the lung. Emphysema occurs in all cases of asthma as a temporary stretching of the lung, physiologic emphysema which disappears when the attack subsides. In organic emphysema the lesion is permanent; it is irreversible. Also, the symptom is persistent and unfortunately irreversible. Meanwhile, Traisman [85] describes death from asthma in an infant aged 12 months. Autopsy showed marked emphysema, but the mucus plugs which are so characteristic of fatal asthma in adults were encountered in only two of the bronchi.

Treatment of Asthma.—On this subject there is nothing really new. Gay and Reinhoff [86] have published the results of bilateral resection of the pulmonary plexus of the vagus nerve. The operation is radical and dangerous, since 6 of the 21 patients died within a week. In 8 of the 21, however, the results were quite successful. Three patients have been restored to almost perfect health, and 5 others are so relieved that they can resume gainful occupations. Potassium iodide, whether given by vein or by mouth, can be demonstrated in the bronchial secretion within fifteen minutes, according to Tuft and Levin.[87] It is excreted by the mucoid cells in the bronchial tree, and it has two actions; the first is to stimulate the smooth muscle of the bronchi, helping them to move the secretion, and the second is to liquefy the secretion and make it less viscid. No wonder potassium iodide is so effective!

Bases and Kurtin [88] find that 6 of 7 patients who died in an attack of asthma were actually suffocated by the secretion in the bronchi, and they suggest that bronchoscopy to remove the block may be life saving. In 1 of their patients bronchoscopy resulted in immediate improvement. It is a timely suggestion.

---

84. Allison, S. T.: The Vanishing Lung: Report of a Case of Advanced Bullous Emphysema, Ann. Int. Med. **17**:139, 1942.

85. Traisman, A. S.: The Pathology of Asthma in Children, Arch. Pediat. **58**:407, 1941.

86. Gay, L. N., and Reinhoff, W. M.: Treatment of Intractable Bronchial Asthma by Bilateral Resection of Pulmonary Plexus: Further Observations, Bull. Johns Hopkins Hosp. **80**:386, 1942.

87. Tuft, L., and Levin, N.: Studies in Expectorant Iodides, Am. J. M. Sc. **203**:717, 1942.

88. Bases, L., and Kurtin, A.: Prevention of Death in Status Asthmaticus: Value of Bronchoscopy, Arch. Otolaryng. **36**:79 (July) 1942.

Other points are of less importance. Maisel and Somkin [89] have added nicotinic acid (niacin) in doses of 0.10 Gm. to the list of those substances which can relieve asthma by intravenous injection. Variations in the potassium intake have been described as important in asthma, but Harsh and Donovan [90] studied the problem and could find no relation between the severity of the symptoms and diets containing as little as 1 Gm. of potassium chloride per day or as much as 18 Gm. per day. Racemic epinephrine is a mixture of equal parts of levorotatory and dextrorotatory substances, according to a report of the Council on Pharmacy and Chemistry of the American Medical Association.[91] Epinephrine U. S. P. is levorotatory and is active; dextrorotatory epinephrine is, however, inactive, so that racemic epinephrine is only half as strong as the conventional product. A true sensitiveness to epinephrine has been described by Dumm,[92] who observed acute urticaria in a patient with asthma after an injection of 0.75 cc. of 1:100 solution of epinephrine hydrochloride. Finally, Vaughan and Graham [93] warn one again concerning the use of morphine in the treatment of asthma. There are two reasons which deserve repetition here. First, morphine depresses the respiratory center and under the influence of the drug the patient may be literally suffocated by the viscid secretion that fills all of his tubes. Secondly, morphine is a parasympathicomimetic drug. A solution of morphine will produce a cutaneous reaction on the arm of a normal person. Morphine can actually cause bronchospasm and so may be the last straw which kills the patient. "After the injection he went to sleep and slept until some one realized that he wasn't breathing any more!"

ECZEMA

The nature of eczema, and particularly the differences between the so-called "atopic eczema" and the so-called "contact dermatitis," are discussed in two excellent articles by Hill.[94] In his practice among infants and young children he encountered and studied 105 cases of

89. Maisel, F. E., and Somkin, E.: Treatment of Asthmatic Paroxysm with Nicotinic Acid, J. Allergy **13**:397, 1942.

90. Harsh, G. F., and Donovan, P. B.: The Effect of Wide Variations in Potassium-Sodium Intake in Asthmatic Children, J. Allergy **13**:105, 1942.

91. Status of Racemic Epinephrine for Oral Inhalation, report of the Council on Pharmacy and Chemistry, J. A. M. A. **120**:287 (Sept. 26) 1942.

92. Dumm, J. F.: Urticarial Reactions in an Asthmatic Patient Following an Injection of Natural Epinephrine, Prensa méd. argent. **28**:303, 1941.

93. Vaughan, W. T., and Graham, W. R.: Death from Asthma: A Warning, J. A. M. A. **119**:556 (June 13) 1942.

94. Hill, L. W.: (*a*) The Classification of Eczematoid Eruptions in Children with Especial Reference to Contact Dermatitis, J. Pediat. **20**:537, 1942; (*b*) The Production of Nonetiological Skin Hypersensitivity to Foods by Natural Means in Atopic Persons, J. Allergy **13**:366, 1942.

atopic eczema and 31 cases of contact dermatitis. Mixtures of the two types are common and present difficult problems. Also, the presence of eczema makes the skin more susceptible to noxious agents of all sorts, particularly to soap and water. Hill's discussions reflect his wisdom, experience and common sense.

Another good paper is by Osborne, Jordan and Hallett [95] who reviewed 120 cases of eczema, finding that foods played a part in not over 10 to 15 per cent. It is interesting to find that factors of dust in the environment, wool, silk, feathers, animal danders, etc., were causes of eczema in the large majority of cases. This is interesting if only because it suggests that absorption through the respiratory tract is quite as important as absorption through the gastrointestinal tract. The observation is correct, but what is the mechanism of this absorption? Can proteins pass through the bronchial or the alveolar epithelium? The questions are proper. In adults dermatitis of the contact type is the important form of eczema. Oliver [96] gives a list of causes met with in industry, as recorded for the United States Public Health Service. They include the following ones: petroleum oil and greases; alkalis, including cement and concrete—producing the so-called "cement itch"; solvents; chromic acid and its salts; metals and plating; dyes; plants; rubber and its compounds; paints and varnishes, and, finally, synthetic resins. The list is long and no doubt will be still longer later. Lane and his co-workers [97] are also interested in industrial and occupational dermatoses and have done much to stimulate interest in this subject. Lane [98] says that a conservative estimate for the country as a whole is about 25,000 new cases of industrial dermatitis a year and that in some industries the development of dermatitis constitutes a serious problem. Meantime, soap is an aggravating factor. At the meeting of the American Medical Association at Atlantic City, N. J., in June 1942, Drs. Lane and Blank [99] presented an exhibit of cutaneous detergents—"Soap substitutes of various kinds which are useful in the treatment of contact dermatitis when soap itself cannot be used." The important points of this exhibit have been published recently. Next in importance to the list of foreign substances met with in industry, and perhaps even more

95. Osborne, E. D.; Jordan, J. W., and Hallett, J. J.: The Practical Management of Eczema in Infants and Children, New York State J. Med. **42**:47, 1942.

96. Oliver, E. A.: Contact Dermatitis, N. Clin. North America **26**:13, 1942.

97. Lane, C. G.; Dennie, C. C.; Downing, J. G.; Foerster, H.; Oliver, E. A., and Sulzberger, M.: Industrial Dermatoses: A Report by the Committee on Industrial Dermatoses of the Section on Dermatology and Syphilology of the American Medical Association, J. A. M. A. **118**:613 (Feb. 21) 1942.

98. Lane, C. G.: The Recognition of Occupational Dermatoses, New England J. Med. **39**:42, 1942.

99. Lane, C. G., and Blank, I. H.: Cutaneous Detergents, J. A. M. A. **118**: 804 (March 7) 1942.

important, is the list of substances occurring in cosmetics and drugs. It is said that 90 per cent of the dermatitis which occurs on the eyelids is caused by nail polish. Nine new cases are described by Palmer.[100] Burgess [101] reports that the active ingredient in nail polish is the basic lacquer made of nitrocellulose but that occasional reactions depend on the coloring matter. Butesin picrate is an old offender, but Boylan [102] reports a new case of extensive dermatitis which complicated a bad burn that was treated with this drug. In a case reported by Laval [103] a patient was treated with a solution of paredrine hydrobromide (p-hydroxy-α-methyl-phenylethylamine hydrobromide) dropped into the eye daily for seventy-nine days. On the eightieth day the concentration was increased from 1 to 3 per cent, and three days later typical conjunctivitis with surrounding dermatitis developed. Bernreiter [104] obtained a positive patch reaction with a 1 : 5 dilution of sodium hydrochlorite in a woman in whom vaginitis developed after she had used a douche which contained sodium hypochlorite (clorox).

Drug Allergy.—This subject also includes a variety of general disturbances. Fox, Gold and Leon [105] describe a severe reaction with fever, flushing, erythema, salivation, nausea and vomiting which followed an intravenous injection of mercupurin into a woman of 27. Phenobarbital caused an exfoliative dermatitis which was fatal in the case reported by Winer and Baer.[106] Kampmeier [107] describes a patient in whom a generalized urticaria developed on each of four attempts to inject tryparsamide into a vein. This led to the practical finding that at Vanderbilt University Hospital 829 patients had been given 43,308 injections of tryparsamide but that urticaria followed in only 5 instances. In none of them did the reaction occur before the ninth dose.

Goldburgh and Baer [108] report the ninth death recorded in the American literature after intravenous administration of diodrast. Do

100. Palmer, R. B.: Dermatitis from Nail Lacquer, Arch. Dermat. & Syph. **44**:13 (July) 1941.

101. Burgess, J. F.: Nail Polish Dermatitis, Canad. M. A. J. **45**:336, 1941.

102. Boylan, C. E.: Butesin Picrate Dermatitis with Case Report, Illinois M. J. **79**:226, 1941.

103. Laval, J.: Allergic Dermatitis and Conjunctivitis from Paredrine Hydrobromide, Arch. Ophth. **26**:585 (Oct.) 1941.

104. Bernreiter, M.: Sodium Hypochlorite Dermatitis, J. Kansas M. Soc. **42**: 424, 1941.

105. Fox, T. T.; Gold, H., and Leon, J.: Hypersensitiveness to A Mercurial Diuretic with Observations on Its Mechanism, J. A. M. A. **119**:1497 (Aug. 29) 1942.

106. Winer, N. J., and Baer, R. L.: Exfoliative Dermatitis Due to Phenobarbital, Arch. Dermat. & Syph. **43**:473 (March) 1941.

107. Kampmeier, R. H.: Urticaria Due to Tryparsamide, Arch. Dermat. & Syph. **44**:671 (Oct.) 1941.

108. Goldburgh, H. L., and Baer, S.: Death Following the Intravenous Administration of Diodrast, J. A. M. A. **118**:1051 (March 28) 1942.

these dreadful experiences mean that intravenous pyelography with diodrast should be abandoned? Far from it! The subject was discussed at a recent meeting of the American Roentgen Ray Society, and it was reported that among 600,000 patients studied by intravenous pyelography with the use of many radiopaque preparations, including diodrast, only 25 deaths had occurred. On the other hand, constitutional reactions, sometimes only a chilly sensation with headache, other times a severe collapse with chills, weakness and impalpable pulse, occur with considerable frequency. Naterman and Robins [109] found that cutaneous tests made by injecting 0.05 cc. of undiluted diodrast into the skin of the forearm gave positive results in 155 of 404 patients. When the drug was given regardless of the result of the test (as it had been given in times past), reactions occurred in 67 patients, or 43 per cent. It is interesting, however, that in the others no reactions occurred, even though the result of the test was positive. The cutaneous test yielded a negative result in 249 of the 404 patients, but nevertheless reactions did occur—in 14 instances. The result of the cutaneous test evidently has a considerable significance, but on the other hand, the test is not infallible. I believe that whenever a foreign substance of complex nature, be it drug or serum, is to be injected into a patient, two simple questions should be asked. The first is "Are you allergic?" (which means: Does this patient have hay fever or asthma or some other manifestation of allergy which indicates that he is likely to have a capacity for the development of sensitiveness to foreign substances?). The second question is "Have you ever had an injection of this substance before?" (which means: Has he had previous treatment which might have sensitized him?). Naterman and Robins found a positive history of allergy in 38, or 9 per cent, of their patients, and 31, or 80 per cent, of these showed positive cutaneous reactions. Unfortunately, the authors do not tell about the relation between the clinical history of allergy and the occurrence of systemic reactions to diodrast.

Reports on reactions to sulfonamide drugs are numerous. Four interesting papers are concerned with reactions to sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). Sams and Capland [110] describe a patient in whom an eczematous dermatitis of the external ear developed after local treatments with sulfathiazole powder. Treatment was omitted, but several weeks later the same man was given 15 grains (0.97 Gm.) of sulfathiazole by mouth. Within four hours an acute dermatitis with massive edema of the face and ears and

109. Naterman, H. L., and Robins, S. A.: Cutaneous Test with Diodrast to Predict Allergic Systemic Reaction from Diodrast Given Intravenously, J. A. M. A. **119**:491 (June 6) 1942.

110. Sams, W. M., and Capland, L.: Topical Treatment with Sulfathiazole, Arch. Dermat. & Syph. **44**:226 (Aug.) 1941.

generalized macular eruptions appeared. Thrombopenic purpura followed medication with sulfathiazole in the case reported by Rosenfeld and Feldman.[111] Rothstein and Cohn[112] had an analogous experience: Acute hemolytic anemia and toxic hepatitis with evidence of damage both to the liver and to the kidneys developed in their patient after treatment with sulfathiazole. The man was extremely ill, but he recovered. Not always, however, does sulfathiazole act on the blood-forming organs. In the 3 cases reported by Dennie[113] pustular and vesicular lesions developed on the hands and feet and later over the whole body. In 1 patient the relation between the lesions and the drug was not recognized at first, and when treatment was continued, swelling of the tongue, with closure of the eyes, developed, and for a time the patient's condition was serious. As Nelson[114] says, the first course of treatment with a sulfonamide preparation is not apt to lead to complications, but if an interval is allowed to lapse, particularly if this interval is only a few weeks or a month in duration, and then the drug is given again, a reaction typical of allergy may occur. Sulfadiazine (2-[para-aminobenzenesulfonamido]-pyrimidine) may also cause reaction. In the case reported by Curry[115] acute agranulocytosis developed in a woman of 41 after prolonged administration of sulfadiazine. What interests me is that this reaction may involve quite different organs in different patients. Keefer[116] also lays stress on this in his excellent review of all the toxic reactions which may follow treatment with a sulfonamide compound. The paper includes a classified bibliography which should be helpful to those persons interested in the subject. In some cases the reaction can be called toxic because it appears on the first dose in a patient who has never had previous contact with the substance. But where there is a story of previous treatment without ill effects and then of an interval before the second course, one has to believe that this first treatment produced a change in the patient to

111. Rosenfeld, S., and Feldman, F.: Thrombopenic Purpura Due to Sulfathiazole, J. A. M. A. **118**:974 (March 21) 1942.

112. Rothstein, I., and Cohn, S.: Acute Hemolytic Anemia Autoagglutination: Toxic Hepatitis and Renal Drainage Following Sulfathiazole Therapy; Case Report, Ann. Int. Med. **16**:152, 1942.

113. Dennie, C. D.: Angioneurotic Edema and Dermatitis Venenata-Like Lesions Due to the Oral Administration of Sulfathiazole, J. A. M. A. **120**:197 (Sept. 19) 1942.

114. Nelson, J.: Acquired Sensitivity to Sulfonamide Drugs, J. A. M. A. **119**: 560 (June 13) 1942.

115. Curry, J. J.: Acute Agranulocytosis Following Sulfadiazine, J. A. M. A. **119**:1502 (Aug. 29) 1942.

116. Keefer, C. S.: Toxic Reactions Following Sulphonamide Treatment, New England J. Med. **226**:266, 1942.

sensitize him in the active and literal sense and so to demonstrate that the severe reactions following the reapplication depend on a change in the recipient rather than on any toxic property of the drug itself.

COMMENT

Once again I have tried to select and comment on those papers published during the last year which seemed to throw some light on the mechanism of allergy. The subject of allergy has been approached from many angles, and at first the various observations seem to be rather isolated. If, however, one turns the pages rapidly to skip many details and to consider the problem as a whole, there is one point which is common to them all.

The nature of the allergic response varies widely among different patients, evidently because different tissues are sensitized to different degrees. Landsteiner showed this in the sensitization of his animals to certain chemicals; Criep's observations on twins demonstrated it; the Arthus phenomenon is obviously a local process. Pollens affect the noses of certain persons and the bronchi of others, and in the case of drugs the wide variation among the manifestations of drug allergy are always impressive. In other words, is it not clear that the symptoms of allergy depend on tissue reactions—in one tissue in 1 patient, in another tissue in another patient? Cutaneous tests are losing some of their glamour, because it appears that tissue sensitiveness may be quite localized, and the tissues involved may or may not include the skin. Such a concept is supported by the marked discrepancies which are observed so commonly. In hay fever, for example, one finds extensive cutaneous reactions in patients who have no symptoms to go with them. And then, on the other hand, as Colmes shows, there are patients who are clinically sensitive but in whom the results of cutaneous tests remain quite negative. In the case of diodrast Naterman finds that in certain patients whose cutaneous reactions to the drug are positive systemic reactions develop when it is injected. But, on the other hand, discrepancies occur in both directions; in some cases the cutaneous reaction was positive, but the treatment was given without reaction, while in a few other cases in which cutaneous tests yielded negative results, the treatment itself caused trouble. It looks, therefore, as though tissues and their reactions constituted the real problem in allergy. Studies of antibodies in the blood are always interesting, but their role is secondary.

The statement "If it was easy, it wouldn't be any fun" applies particularly to the study of allergy.

263 Beacon Street.

Book Reviews

El corazon y la circulacion en los hipertiroideos. By Héctor Gotta, M.D. Pp. 103, with 13 plates. Buenos Aires: Sebastian Amorrortu e Hijos, 1938.

The author has prepared this book as a contribution to the study of the unsolved problems of hyperthyroidism. Its nine chapters begin with a study of the precordial area of patients who have hyperthyroidism, a study which in 1938 was published as a paper in the ARCHIVES OF INTERNAL MEDICINE (Gotta, H.: Size and Shape of the Heart in Hyperthyroidism, ARCH. INT. MED. **41**:860 [June] 1938). In the second chapter the shape of the heart of patients who have exophthalmic goiter is considered. The author finds that 33 per cent of patients with this disorder have a prominent left middle arc as an outstanding abnormal feature in the general configuration of the heart. This percentage decreases as age progresses, and the abnormality never has been noted to appear during the course of the disease or to disappear after complete recovery of the patient. Therefore, it must be considered to be a constitutional element, the author thinks, probably characteristic of persons in whom there is a tendency for the thyroid to become hyperfunctioning.

Electrocardiographic changes are discussed on the basis of study of 203 patients on whom 305 tracings were made. Full consideration of the subject led the author to the conclusion that there are not constant or specific variations in the tracings of patients who have exophthalmic goiter. The particular instance of the negative T wave in leads II and III, as encountered previously by Willius and Boothby in 3 patients, does not necessarily constitute a contraindication to thyroidectomy or an unfavorable prognosis.

Particular attention is given to auricular fibrillation associated with hyperthyroidism. The author feels that hyperthyroidism itself is an important factor in the production of such fibrillation, but because its frequency increases with the age of the patient, the author thinks that arteriosclerosis and hypertension also should be considered. As a general rule, he said, patients who have exophthalmic goiter and auricular fibrillation should be examined for associated cardiovascular disease, which usually is responsible for the enlargement of the precordial area that is encountered in a good number of cases. Subtotal thyroidectomy actually is the best treatment of auricular fibrillation in exophthalmic goiter; iodine and digitalis are the most helpful drugs to administer during the preoperative and postoperative periods, and quinidine has exceptional value in cases of persistent fibrillation after surgical removal of an adequate amount of glandular tissue.

In regard to blood pressure the author finds that an increased differential tendon occurs as a result of elevation of the systolic pressure and decrease of the diastolic pressure, the latter being more constant and more noticeable. Usually, he said, after cure of the hyperthyroidism, blood pressure returns to the values which obtained previous to the onset of the disease.

In discussing anatomic and physiologic aspects of the circulation in the presence of exophthalmic goiter the author places himself with those investigators who believe that hyperfunctioning of the thyroid gland does not produce specific or organic lesions of the myocardium. He thinks there are good reasons to consider the cardiac disturbances encountered in cases of this condition as purely functional disturbances.

Angina pectoris and cardiac failure frequently are associated with hyperthyroidism, and Gotta believes that in these conditions hyperfunction of the thyroid gland is an important precipitating factor. He remarked that a weak heart is not a contraindication to the surgical treatment of exophthalmic goiter; on the contrary, he declares it is an adequate indication for thyroidectomy.

A complete bibliography and a brief index constitute the final pages of this interesting monograph. It is well printed and thoroughly readable, and undoubtedly it will prove of considerable value to persons especially interested in cardiovascular and endocrine diseases.

Internal Medicine in Old Age. By Albert Müller-Deham, M.D., and S. Milton Rabson, M.D. Price, $5. Pp. 396. Baltimore: Williams & Wilkins Co., 1942.

It hardly seems necessary to comment on a fact now well recognized, that gerontology is becoming an ever increasingly important division of medicine. The science of the changes, both physiologic and pathologic, that take place in the body of an aging person will naturally demand greater attention from members of the medical profession as human longevity becomes more and more extended. To meet the needs of practitioners there will be appearing from time to time books dealing with geriatrics. It is not entirely improbable that ultimately there may be as many textbooks, reference books and encyclopedias on the subject of old age as there are on pediatrics.

According to the preface, the authors of "Internal Medicine in Old Age" have for many years been interested in old patients. The senior author spent some fifteen years in Vienna and observed no less than 2,000 necropsies on elderly persons, as well as seeing these persons while alive. The junior author has likewise studied the pathology of senility for many years. The authors seem well qualified to prepare a book on this subject.

The first seven chapters have to do with general physiologic, hygienic and statistical facts of longevity. Then follows a series of chapters on the changes induced by aging in the respiratory system, the cardiovascular system, the urogenital system and the digestive system, with one chapter on blood dyscrasias, another on endocrine disorders, two on metabolism, three on the musculoskeletal system and one on infectious diseases. The greatest amount of space is devoted to the digestive system, a few more pages than those dealing with the cardiovascular system. There seems to be a disproportionate amount of space given to the digestive system in contrast to that given to the heart and blood vessels. It may be true, however, that old persons suffer from diseases of the digestive system and die of diseases of the cardiovascular apparatus. A disproportionately small amount of space is given to endocrine disorders, which are, after all, common in aged persons. The glands of internal secretion, which make up one division of the human system, practically always show the effects of old age to a greater or lesser degree, more often the former.

The book is thought provoking, well organized and well documented. In spite of the feeling of many physicians that not much can be done medically for old persons, the authors have given a considerable amount of space to the treatment of the various diseases they describe. The material on treatment is sufficiently specific to satisfy a practitioner who wants to know what to do for an old person who has intermittent claudication, diarrhea, paroxysmal dyspnea, nephritis, hypertension and so on. It might be added that the authors have not only written fully on what should be done but have wisely given considerable thought and space to what should not be done for elderly patients.

Advances in Pediatrics. Edited by Adolph G. De Sanctis, M.D. Associate Editors: L. Emmett Holt, M.D.; A. Graeme Mitchell, M.D.; Robert A. Strong, M.D., and Frederick F. Tisdall, M.D. Price, $4.50. Pp. 306. New York: Interscience Publishers, Inc., 1942.

The editors have compiled a collection of the most significant contributions to pediatric literature which have appeared during the past two years. Continuance of this volume as an annual review is proposed.

The book includes ten sections by various authors as follows: Toxoplasmosis: A Recently Recognized Disease of Human Beings, by Albert B. Sabin; Review of Virus Diseases, by Horace L. Hodes; Chemotherapy in Diseases of Infancy

and Childhood, by Benjamin W. Carey; Electroencephalography, by Major Normal Q. Brill; The Role of Vitmin K in Hemorrhage in the Newborn Period, by H. G. Poncher; Persistent Ductus Arteriosus and Its Surgical Treatment, by Robert E. Gross; The Premature Infant, by Abraham Tow; Tuberculosis, by Waldo E. Nelson; Endocrinology, by Murray B. Gordon, and Short Abstracts of Some Other Advances in Pediatrics, by Adolph G. De Sanctis and George E. Pittinos.

The volume will undoubtedly be of greatest value to those persons who find it impossible to cover the current pediatric literature as it appears. The reviewer feels that in general the various articles could be presented in a much more condensed form, particularly since the original work has been published so recently and is so readily available.

The section on Toxoplasmosis, by Dr. Albert B. Sabin, rightly stands first in the volume as the most lucid and interesting contribution. Some subjects, such as cystic fibrosis of the pancreas, influenzal meningitis and the prophylactic use of sulfanilamide in rheumatic fever, seem to deserve more detailed coverage than is accorded them in the short abstracts in the final section.

"Advances in Pediatrics" should prove to be of inestimable value to the busy practitioner.

Blood Substitutes and Blood Transfusion. By Stuart Mudd, M.A., M.D., professor of bacteriology, University of Pennsylvania School of Medicine, Philadelphia, and William Thalhimer, M.D., director, Human Serum Division Public Health Research Institute of the City of New York, Inc. First edition. Hammermill straw. Price $5. Pp. 407. Springfield, Ill.: Charles C Thomas, 1942.

This symposium-monograph is the work of many authors. Many of the papers were presented at the annual meeting of the American Human Serum Association held in June 1941, at Cleveland. Any advance work done on the particular subjects were included when the proofs were read this spring. The book is filled with information, interesting and valuable not only to the specialist, but also to the individual who is seeking an answer to many of the present day questions relating to whole citrated blood, blood plasma, blood serum and other blood substitutes. The book is ably summarized in the last chapter, "successful management of shock requires early recognition and effective measures for breaking the vicious circle. These will be directed toward removing the cause, toward increasing the blood volume and toward relieving anoxia." The four general methods of preserving plasma and serum are discussed. Points for and against each method are given. The merits of hemoglobin, serum albumin and casein digest as blood substitutes are discussed. The storage, transportation and administration of whole blood is ably presented. The Rh factor is discussed in a readily understandable manner. The specific A and B factors are shown to neutralize the anti-A and anti-B isoagglutinins found in group O blood. Reasons for and against the use of group O blood as from a universal donor are presented. On the whole, the book is interesting, informative and of value to general practitioner and specialist alike.

Blutdruckmessung und Kreislauf in den Arterien des Menschen. By Heinrich von Recklinghausen. Pp. 532, with 197 figures. Leipzig: Theodor Steinkopff, 1940.

This amazing book is an exhaustive treatise on the theoretic and laboratory aspects of the human pulse and blood pressure. It would be difficult to discover any omissions of mathematical, physical or historical material; the book is evidently the result of a lifetime of patient collecting of material relating to hemodynamics. Every imaginable type of sphygmographic and sphygmomanometric device is illustrated and discussed. The historical notes are interesting and bear

witness not only to the cooperation of investigators of many different countries in advancing hemodynamics but to the broadness of the author's perspective.

The book does not concern itself with questions of pathogenesis, diagnosis or biometry such as might arise, for instance, in life insurance work; consequently, its use to a practicing physician would be limited to occasional reference, for instance, on the construction and use of instruments like Pachon's oscillometer in cases of peripheral vascular disease. But for any one planning laboratory research in hemodynamics or wishing to devise new sphygmographic apparatus, many portions of this book would be of fundamental importance.

Changes in the Knee Joint at Various Ages. By Granville A. Bennett. Hans Waine and Walter Bauer. Price, $2.50. Pp. 97, with 31 plates. New York: The Commonwealth Fund, 1942.

This handsome volume contains the results of part of a large research project on arthritis sponsored by the Commonwealth Fund, the Massachusetts Department of Public Health and the Robert W. Lovett Memorial Fundation. The original work deals with changes in the knee joint at various ages, but the volume really is a comprehensive treatise on "degenerative" arthritis. The interesting point is brought out that after the second decade degenerative changes in the knee joint become common. There are a full bibliography, beautiful plates and an adequate index.

Cabot and Adams—Physical Diagnosis. By F. Dennette Adams. Price, $5. Pp. 888, with 398 illustrations. Baltimore: The Williams & Wilkins Co., 1942.

In this thirteenth edition, under the editorship of Dr. Adams, Cabot's physical diagnosis carries on in able fashion. It is an interesting comment on modern specializations that the editor has called on consultants in various fields, so that what was originally a decidedly one man book now becomes to some extent a summation of the views of a group. Certainly in this process nothing of readability and usefulness has been lost.

The Biological Action of the Vitamins. Edited by E. A. Evans Jr. Price, $3. Pp. 227. Chicago: University of Chicago Press, 1942.

This volume is a collection of fourteen papers on various subjects connected with nutrition and vitamins presented at a symposium held during the anniversary celebration of the University of Chicago. That the authors of the various contributions include such men as Elvehjem, Jolliffe, György, Sebrell and Lepkowsky testifies to the quality of the papers.

Introduction to Parasitology. By A. S. Pearse. Price, $3.75. Pp. 357, with 448 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1942.

This book, written from the biologic standpoint, seems to the reviewer to fill a real need of the practicing physician. Here in simple terms is a systematic discussion of parasites not only of man but of animals. The human parasitology is fitted into a sound general background. The numerous illustrations are an outstanding feature.